

Chapter 7

Clinical Discussion: Experiences in Assessment and Treatment

In the majority of individuals, depression is the result of a confluence of multiple predisposing antecedent factors (e.g., genetics, developmental influences and learning, environmental exposures, cultural conditioning, trauma, lifestyle) and more immediate triggers (e.g., divorce, job loss, death of a loved one). There may also be mediating factors that make recovery difficult, such as poverty, chronic pain, or other illness. The depressive process is mediated on the metabolic level by multiple chemical messengers including (but not limited to) neurotransmitters, receptors, second messengers, cytokines, neuropeptides, and hormones.

In most instances, the depressive disorder is not precipitated by a single trigger. Rather, it occurs when antecedents (e.g., genetic vulnerabilities) and life event triggers intersect and interact with dysregulated systems and processes. As an individual experiences more episodes of depression, a kindling process is thought to occur¹ in a significant number of people. The ability to be sensitized or kindled is a property of the central and peripheral nervous system in which, over time and repeated exposure, less and less of a stimulus is needed to evoke a given response. Ultimately, as a result of neuromodulation, a response such as depression may occur in the absence of any stimulus.² However, this kindling process may be context dependent³ and thus modifiable by significant changes in one's context.

Clinical Pearl:

The person with depression is in a complex homeostatic state, albeit a disturbed, negative, painful one. The task of the clinician is to develop an understanding of the homeostatic processes (social, environmental, biological) involved and identify the points that require intervention. The clinician must then intervene at *as many of these points as possible at the same time* to re-establish a new, more functional equilibrium. The ability of the clinician to intervene at multiple points often depends on the resources available both to the patient (e.g., emotional, practical, and financial support) and the clinician (e.g., time, staff support). Assessing resource availability, therefore, is critical—the skills for doing this effectively develop over time, as does the clinician's awareness about the impact of socio-cultural factors on both the cause and cure of depression.

The Functional Medicine Matrix Model (see Figure 6.1 in Chapter 6) shows how symptoms, antecedents, triggers, and mediators of disease can be integrated in an organized process that simultaneously evaluates underlying dysfunctions and identifies the most disordered systems. This process and the clinical strategies that flow out of it work ex-

tremely well for the evaluation and treatment of depression (and many other chronic diseases). The discussions that follow are thus organized using the functional medicine paradigm, which is fundamentally a systems approach.

Clinical Pearl:

Neurotransmitters are built using several essential nutrients (e.g., tryptophan, tyrosine, folic acid, B12, magnesium, copper) that must be available in adequate supply. High neurotransmitter demand (due, for example, to physical/emotional stress or use of stimulants or other medications such as H2 receptor blockers, which reduce parietal cell output and therefore decrease the absorption of B12) increases the need for these essential nutrients. If any of them are in short supply, neurotransmitter production and maintenance of a steady state are impaired. In addition, the breakdown, absorption, and recirculation of the neurotransmitters are nutrient-dependent processes, requiring folic acid and methionine, for example. They are also dependent on enzymes known to be affected by genetic SNPs (e.g., COMT, MTHFR). *Key tasks for the clinician are: (1) to assess the adequacy of diet (nutritional value of the food sources), digestion, and absorption of the key ingredients used to make and utilize neurotransmitters, and (2) to maximize the efficiency with which these systems work, even in the face of genetic limitations.*

Structuring the Clinical Management of Depression: A Systems Approach

The prevailing conventional paradigm for assessing and treating depression focuses exclusively on dysregulation in (a) neurophysiology, as it affects mood, reward, vegetative function, the stress response system, and cognitive function, and (b) psychosocial function. This model acknowledges in theory the possible relevance of many elements of the Functional Medicine Matrix but has not integrated them into clinical practice, despite the large and growing evidence base that would support such a step. In my opinion, there are many reasons for this failure of mainstream medicine to adopt and adapt, including:

- The continuing power of the excitement generated in the 1950s by the impressive results of psychopharmacology, bolstered by the huge profits generated by sales of these medications
- The influence of the pharmaceutical industry on the direction of research into mood disorders and also on medical education, where a great deal of money is in play to advance the pharmaceutical model
- The managed-care model, which has concluded that the use of pharmaceuticals is the most cost-effective treatment for depression (despite the evidence presented in this monograph indicating that more than 50% of people treated with this model fail to recover fully)
- The pervasive sense of time pressure in both individuals and corporations within Western culture, creating demand for both fast food and fast cures
- The success of the acute-care model, leading to inappropriate approaches for chronic illness
- The fact that conventional medicine has long operated primarily from a mechanistic and reductionist model in which all we need to understand human health is to study the individual parts of the human organism; however, a better understanding of health and disease will require of all of us a much more comprehensive knowledge of the interactions and interconnections among all aspects of the mind-body-spirit totality.

As the previous chapters document, there is a substantial body of mainstream research, often ignored by conventional medicine, supporting both the need for and the efficacy of a more comprehensive approach to depression. In this advanced paradigm, depression is conceptualized as *the product of a reverberating, multidirectional dysregulation in various aspects of the Functional Medicine Matrix, encompassing a large number of antecedents, triggers, and mediators.* In a sense, believing and acting as though depression were a serotonin deficiency is analogous to believing that the world is flat. It is only a matter of time before the interconnectedness of our physical, mental, emotional, spiritual, socioeconomic, cultural and ecological systems is reflected in the treatment of depression.

In our new model, a systems approach is used to gather a full picture of the patient's situation. The clinician must circle around the problems, using different lenses with different powers of magnification and focus, different assessment tools, and expanded attention to the patient's story in order to arrive at a fuller understanding of the underlying dysfunctions.

The Interview: Critical Steps in Eliciting the Depressed Patient's Story

First, of course, the basic information must be obtained:

- Current prescribed and over-the-counter medications, including dosages/durations/benefits and side effects
- Supplements
- Vital signs, including height, weight, changes in weight over time, and reported blood pressure
- Full review of systems to elicit any additional and possibly related complaints and conditions

Clinical Pearl:

Frequently, collateral history can be critical in altering the diagnostic impression and prognosis. Many of the interview questions suggested can be very useful in establishing: (1) level of pre-morbid function, (2) level of childhood function, (3) family psychiatric history, and (4) history of hypomania or mania, to be certain one is not overlooking a bipolar disorder. If all the information is not obtainable in person at the interview, it may be possible to speak with someone the patient trusts, preferably someone who has known the patient for some time, to obtain a different perspective and/or additional information about these issues.

Once the basic information has been elicited, the clinician can ask the patient, "If there were one thing I could help you with, what would that be?" Using the answer to this question, the clinician generates a problem list, and then takes the history of each problem. In the case of depression, it is critical to:

- Get a history of the current episode, including a careful assessment of the precipitating stressors.
- Get a clear history of the first episode and discover whether the depression is episodic, with a certain frequency/duration.
- Ascertain the pre-morbid condition (was there low level anxiety or depression already?), and find out whether there was a significant antecedent to the first episode; "When was the last time you felt really well? What happened next?"
- Find out whether there are usually precipitating triggers; the more episodes one has, the less likely they are to be precipitated by events and the more likely they are to be autonomous or kindled.
- Assess all of the symptoms of the current episode, including suicidality.⁴
- Assess whether this is a hyperadrenergic/hypercortisolemic (melancholic) depression or a hypoadrenergic/hypocortisolemic (atypical) depression, or perhaps a combination. (See *Clinical Interventions* below.)
- Discover what treatments have been tried (dosage, duration, response, side effects); having the patient's pharmacy print out a complete record assists in this process.
- Assess the patient's sense of helplessness and hopelessness, and find out what it is centered around (e.g., the need for power/control, the need to be loved or to perceive oneself as loving⁵).
- Assess the level of anxiety and panic, as these are often implicated in suicide risk.

While attending to the above, many other important aspects of the patient's history and condition must also be assessed, as described below.

Temperament

Temperament is essentially inborn and only minimally modifiable by experience and caregivers. It is distinguished from character (self-direction and the ability to cooperate), which is modifiable. Together, temperament and character comprise what we think of as personality. (See *Understanding Biological Psychiatry*² for a brief but clinically relevant discussion of temperament.) Certain important characteristics of temperament can be evaluated by inquiring about the following:

- Harm avoidance
 - Does the patient experience increased reactivity to a novel stimulus?
 - Is change difficult?
 - Does the patient avoid change or novel situations?
 - Does the patient consider himself or herself emotionally sensitive or emotionally reactive?
- Novelty seeking
 - Is intense exhilaration experienced in response to a new situation or a novel stimulus?
 - Is the patient a thrill seeker?
 - Is the patient intolerant of structure and monotony, regardless of the consequences?
 - Does the patient like unpredictability?
 - Are the patient's relationships and work disorganized and in flux?
 - Does the patient get bored easily?
- Reward dependence
 - Is the patient dependent on social support?
 - Is the patient a hard, industrious worker who works until exhaustion?
 - Is the patient sensitive to rejection?
 - Does the patient feel that he or she has an "addictive personality"?
 - Does the patient get cravings for things or situations that give pleasure?
 - Does the patient continue to engage in behaviors or relationships that used to be rewarding, even though they are no longer rewarding or are even harmful?
- Impulsivity
 - Has the patient done things impulsively in the past, which he or she looks back on and questions? What are some examples?

Neurotransmitter Function

Different neurotransmitter systems (hundreds of substances are involved in neurotransmission) overlap and interact, so this approach is only an approximation, at best. Table 7.1 provides a brief overview of some clinical correlates of neurotransmitter function. Diagnostic categories, while useful in many ways, are merely labels. A person can have many labels, but perhaps only one or two neurochemical abnormalities. The neurotransmitter assessment should include:

- Serotonin — Serotonin dysregulation is associated with depression, mania, obsessiveness, obsessive-compulsive disorders, trouble changing focus, cognitive inflexibility, anxiety, mood disturbance, irritable bowel syndrome (IBS), migraine, chronic pain, impulsivity, eating disorders, and perfectionism.
- Norepinephrine — Central norepinephrine activity (generated in the locus coeruleus) is increased in melancholic depression, panic disorder, and anxiety; it is decreased in atypical depression and ADD/hyperactivity in a variety of specific areas of the brain (e.g., portions of the prefrontal cortex).
- Epinephrine — This neurotransmitter can be measured in a 24-hour urine test, which reflects total body status; low levels may be associated with low blood pressure, orthostasis, slow pulse, easy fatigue, chronic stress, or inadequate nutrition.

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- Dopamine — High urinary (total body) levels are associated with intense anxiety, psychosis, certain cases of obsessive-compulsive disorder; low levels are associated with depressive symptoms (lack of motivation, decreased libido, anhedonia, apathy) and perhaps ADD.
- GABA — Downregulation of GABA is associated with anxiety, panic, seizures, and depression.
- Glutamate — Look for hypersensitivity to MSG, evidence of hyperexcitability, cognitive dysfunction (Alzheimer's, Parkinson's), psychosis, hypoglycemia, seizure, all of which can be associated with excess N-methyl-D-aspartate (NMDA) receptor activation by glutamate.

Table 7.1—Neurotransmitters of Known Importance in Biological Psychiatry

Neurotransmitter	Type	Derived From	Clinical Associations
GABA	Amino acid	Glutamate	The most ubiquitous amino acid in the central nervous system. Involved in sleep, anxiety reduction, muscle relaxation, mood.
L-Tryptophan	Amino acid	Can be obtained in the diet or through supplementation	Promotes sleep, especially when taken with a high-carbohydrate, low-protein meal. Converts into serotonin, melatonin; can be shunted via alternate pathways away from serotonin production. Dangerous when consumed with monoamine oxidase inhibitors or even SSRIs and SNRIs.
Tyramine	Amino acid	Protein	Dangerous when consumed with monoamine oxidase inhibitors.
Glutamate	Amino acid	Protein	The major excitatory amino acid. Excess (e.g., delirium tremens) is associated with neurotoxicity. Dysregulated in psychotic disorders and probably in mood disorders. Linked with nitric oxide function and NMDA receptors.
Dopamine	Biogenic amine	Tyrosine, fats, carbohydrates	Associated with mood disorders, anhedonia (absence of pleasure), apathy, blood pressure regulation, as well as schizophrenia, Parkinson's disease, ADD, substance abuse, tics.
Norepinephrine	Biogenic amine	Dopamine	Associated with blood pressure regulation and necessary for learning and memory. Probably involved in post-traumatic stress disorder, anxiety, and panic.
Serotonin (5-HT)	Biogenic amine	L-tryptophan	Associated with blood pressure and temperature regulation, gastrointestinal function, vascular and platelet function, mood disorders, and a host of conditions mentioned above.

Sleep

The clinician's interview should assess the following:

- Total amount of daily sleep.
- Initial, middle, or terminal insomnia — If initial insomnia, what keeps the patient awake, obsessing, fear, too much energy, pain, hypoglycemia, restless legs?
- Hypersomnia.
- Decreased REM latency — One of the best markers of depression, but also present in narcolepsy; the clinician should ask the patient, "If you fall asleep during a brief nap, might you be dreaming when you wake? Do you remember your dreams?"
- Sleep deprivation.
- Narcolepsy — Extreme daytime sleepiness (e.g., when driving or upset); also may involve sudden REM onset, sleep paralysis (very vivid dreams in which the person is usually terrified and aware that they are awake, but cannot move), loss of muscle control, and family history.

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- Sleep apnea — Associated with increased abdominal weight and blood pressure, testosterone use, snoring, waking up with headache, waking in the middle of the night gasping for breath, and central nervous system (CNS) lesions (e.g., vascular lesions); frequently necessary to ask whether bed partners have complained; it is critical to identify sleep apnea, as untreated it can lead to obesity, cardiovascular disease, stroke, dementia, and, of course, low energy.
- Paroxysmal nocturnal myoclonus (periodic leg movements of sleep, PLMS) — The clinician should ask whether the patient has been known to kick at night while asleep, whether the bedsheets are a mess in the morning, and whether the patient wakes refreshed.
- Delayed sleep phase — The timing of the sleep cycle should be assessed.
- REM sleep behavior disorder — Complex behaviors occurring during sleep that can be indicative of central noradrenergic dysfunction and should be evaluated further.

If indicated based on the history obtained through these questions, the patient should undergo the appropriate sleep study (e.g., overnight polysomnography or multiple sleep latency testing).

Family Psychiatric History

- The clinician should make a family tree for both maternal and paternal sides, including as many generations as possible, then question whether each and every family member has had:
 - Moodiness/aggression
 - Depression
 - Physical, emotional, or sexual abuse, particularly in the family of origin
 - Extreme success, perhaps followed by extreme losses (suggestive of bipolar disorder)
 - Psychosis
 - Unusual lifestyles
 - Migraines (associated with depression)
 - Obesity/eating disorders
 - ADD or learning disabilities
 - Alcohol or drug problems
 - Suicide attempts
 - Diseases associated with affective disorders, including heart disease, osteoporosis, or diabetes (see Chapter 3, *Epidemiology and Public Health Impact*)
 - Unusual creativity, which can be associated with mania/hypomania or can be an early sign of fronto-temporal dementia
- The cause of death and age at death for grandparents, parents, children, siblings, aunts, and uncles should be obtained.
- The clinician should ask about the number of marriages and children; frequent marriages can be an indicator of affective instability and perhaps bipolarity.
- The clinician should ask about the patient's home environment as a child. Were the parents in frequent conflict? If so, was it physical or verbal? Who was the target? Was the patient afraid at home as a child?

Personal History

- What was the patient's birth history? Any prematurity, trauma, or colic?
- Were the childhood developmental milestones within normal limits?
- How did the patient do in school?
- Was the patient very shy?

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- Did the patient experience separation anxiety to the degree that it was difficult to go to kindergarten, first grade, or summer camp?
- Was the patient able to do homework, or did he or she procrastinate on larger projects?
- Did the patient have many friends?
- Did the patient feel as though he or she fit in with other children?
- Was the patient the target of bullying (social defeat model of depression)?
- How far did the patient go in school?
- What were the patient's hobbies?
- What excites the patient?
- When was the patient happiest in life? What were the ingredients of that happiness (e.g., physical, spiritual, social, intellectual elements)?
- Does the patient have many close friends now?
- What is the patient's social network like at this point?
- What is the patient's spiritual/religious involvement? Is it satisfying?
- Is there a history of physical, sexual, and/or emotional abuse?
- Has the patient experienced frequent or significant moves or social displacement?

Neurological History

Collateral history is extremely important here, and it is absolutely vital to clarify all issues that arise as a result of this portion of the interview. Positive responses to these questions should lead the clinician to wonder about temporal lobe dysfunction, if not an outright seizure disorder (e.g., partial complex seizures without loss of consciousness), and to consider the implications for pharmacological treatment. For example, most antidepressants would cause such a patient to feel agitated and worse, and thus antidepressants would be contraindicated—at least until the temporal lobe dysregulation is stabilized.

- Is there a family history of seizures?
- Does the patient experience rage or irritability in excess or without a clear reason?
- If there is irritability, is it followed by exhaustion and/or lapses in memory?
- Does the patient ever smell things that are not there?
- Does the patient have unusual sensory experiences or spiritual experiences?
- Does the patient feel suspicious of people?
- Has the patient ever had a seizure with a very high temperature as a child?
- Has the patient ever lost consciousness? If so, in what way, for how long, and how often?
- Has there been any head trauma?
- Does the patient ever experience a blank in time? For example, one can ask, "Did you ever have the experience of knowing that one minute it is 2 PM and the next thing you know it is 2:30, and you have absolutely no recollection of the passage of time?"
- Does the patient ever find evidence that he or she has done something but has no recollection of doing it?
- Does the patient ever see or feel things or his or her body (e.g., hands) as being distorted in size so that they appear or feel very large and close up or small and far away?
- Are there déjà vu experiences? With what frequency?
- Are there jamais vu experiences? With what frequency?
- Have there been any MRIs or brain scans? If so, why was it ordered, and was it normal?
- Has the patient ever had an EEG? If so, why was it ordered, and was it normal?

Standardized Depression Assessment

A standardized measure of depression such as the Beck Depression Inventory¹¹ should be used. The clinician can get a baseline measure, done by the patient before the initial interview, and follow up periodically to provide an objective assessment of progress.

Conditions to Rule Out

As the interview progresses, the clinician should develop a list of the standard medical conditions he or she wishes to rule out, such as porphyria, tick-borne disease, complex partial seizures without loss of consciousness (temporal lobe epilepsy), sleep apnea, paroxysmal nocturnal myoclonus, hypochlorhydria, pernicious anemia, and small intestine bacterial overgrowth (SIBO), then make a plan for evaluating each condition on the list.

Clinical Pearl:

Be cautious about labeling someone with a personality disorder because many patients successfully treated for their affective disorder do not show any personality disorder once recovered.^{6,7}

Using the Functional Medicine Matrix Model

Collecting, evaluating, and reflecting upon the above fairly standard information should be followed by a comprehensive functional medicine assessment. Through a careful review of the information gleaned from the interview process, patient questionnaires, or other tools (e.g., Beck Depression Inventory), the clinician will begin to identify the systems that are dysregulated in each patient. Table 7.2 provides a list of systems often dysregulated in depression.

Table 7.2—Systems Dysregulated in Depression

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- **Current paradigm:**
 - Mood (euphoria/elation vs. irritability/depression)
 - Reward/pleasure vs. inhibition/punishment
 - Vegetative functions (appetite, wakefulness, circadian rhythm)
 - Reproductive functions (libido)
 - Motor functions (impaired coordination/activity level)
 - Cognition (memory, concentration, judgement)
 - Relational characteristics (isolation vs. interaction)
 - Psychosocial characteristics
 - **Advanced functional medicine paradigm (systems-oriented perspective):**
 - Immune surveillance
 - Oxidative/reductive homeodynamics
 - Inflammatory process
 - Digestion, absorption, and barrier integrity
 - Detoxification and biotransformation
 - Structural integrity
 - Psychological and spiritual equilibrium
 - Hormone and neurotransmitter regulation
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The remainder of this chapter is organized into 3 main topics that will lead to an understanding of a functional medicine assessment:

- A — Assessment Strategies
- B — Clinical Interventions
- C — Practical Implications and Considerations

¹¹ The Beck Depression Inventory is copyrighted and can be purchased at harcourtassessment.com; a copy may be reviewed at http://www.ibogaine.desk.nl/graphics/3639b1c_23.pdf.

A — Assessment Strategies

Laboratory and other tests will help the clinician detect important dysfunctions in the depressed patient. Individualized clinical interventions in the areas of the Functional Medicine Matrix (as indicated by the clinical and laboratory evaluation process) will promote improved response and recovery for a significant percentage of nonresponsive and partially responsive depressed patients, when compared with the current conventional model alone.

Comprehensive Workup (Baseline)

The following tests should be done *fasting* in the early morning in all patients with depression.

1. Blood

- Complete blood count (CBC) with differential
- Chem 24 — Includes liver function (AST, ALT, AlkPhos), electrolytes (K+, Cl-, Co2, Na), glucose, calcium, total protein, calculated globulin, albumin, A:G ratio, total bilirubin, BUN, creatinine, BUN-creatinine ratio
- Thyroid levels — Free T3, free T4, TSH, and reverse T3
- Homocysteine
- Insulin
- MTHFR genetic polymorphism (C677T polymorphism)
- COMT genetic polymorphism
- Plasma amino acid analysis
- Red blood cell mineral analysis
- 1,25-hydroxy vitamin D and 25-hydroxy vitamin D
- Intracellular nutrient analysis for B vitamins
- Red blood cell essential fatty acid analysis
- Lipid panel
- Serum adrenocorticotrophic hormone (ACTH)

2. **Saliva** — Adrenal salivary cortisol index (adrenal stress index, or ASI) measures cortisol and DHEA output from the adrenal glands (measured at 7–8 AM, 11 AM–noon, 3–4 PM, and 11 PM–midnight); test is highly sensitive^{8,9}

3. **Urine** — 24-hour urine test for catecholamines (e.g., epinephrine, norepinephrine, dopamine) and 5-hydroxyindole acetic acid (5-HIAA); the lab should provide the patient with dietary instructions to exclude substances such as caffeine, stimulants, and certain fruits such as bananas

4. Other

- Body mass index and weight
- 3-day diet history
- Exercise history
- Temperature testing — 3 days, 3 times daily (in the first half of the cycle in menstruating females)

Additional Assessment Options (as warranted)

1. **Digestion, Absorption, and Barrier Integrity** (if there appears to be a gastrointestinal or digestive problem)
 - Digestive stool analysis — Includes markers that test for digestion, absorption, inflammation, adiposity, exocrine pancreatic function, dysbiosis, occult blood, ova and parasites, immunology, and pH
 - IgG delayed food sensitivity test

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- Dental exam — Has the patient had root canals, which can result in low-grade chronic infections (that the patient will not feel since the nerve root has been destroyed), causing chronically elevated cytokine levels? Does the patient have gum disease or untreated dental caries?
 - Breath test¹⁰ — Simple, noninvasive test that can be considered to rule out SIBO, if symptoms (e.g., belching after meals, constipation, bloating, signs of malabsorption, a sense of prolonged fullness after meals) warrant; the breath test measures both hydrogen and methane produced by bacteria in the small intestine, and higher levels of these gases in the breath indicate bacterial overgrowth in the small intestine
- 2. Immune Surveillance/Inflammation/Infectious Process** (if there appears to be an immune or inflammatory problem)
- If infection is suspected, the source/type of infection should be identified (e.g., SIBO, recurrent/chronic sinusitis, tick-borne diseases such as Lyme [chronic Lyme often presents with reduced CD57 cell count], *Babesia*, *Bartonella*, *Anaplasma*, *Mycoplasma*, EBV, HIV, human herpes viruses, hepatitis), and natural killer (NK) cell activity should be tested; antiphosphatidyl serine (IgM) antibodies, MMP-9, angiotensin converting enzyme (ACE), and an elevated 25-hydroxy:1,25-hydroxy vitamin D ratio (see below) can be indirect indicators of chronic inflammation/infection
 - IgG and IgE testing for food and respiratory allergies
 - Erythrocyte sedimentation rate
 - CRP (highly sensitive)
 - 24-hour challenge test for heavy metals
 - ANA or other autoantibodies testing, depending on syndrome, history, and physical
 - Comprehensive digestive stool analysis, depending on history and physical
 - Eosinophil count, platelets (in CBC)
 - Eosinophil protein x and calprotectin (on stool testing)
 - 25-hydroxy:1,25-hydroxy vitamin D ratio — The active form of the vitamin D hormone (1,25-OH) is present in excessive levels relative to the inactive form (25-OH) in patients diagnosed with inflammatory illnesses such as certain autoimmune illnesses, chronic fatigue syndrome, fibromyalgia, and tick-borne diseases (e.g., Lyme disease); evidence suggests that this is due to unregulated production of 1,25-hydroxy vitamin D by macrophages in the course of an excessive Th1 immune response¹¹; a ratio greater than 1.5 can indicate an infectious process (e.g., chronic mycobacterial infection, Lyme borreliosis), in which the T helper cell balance (Th1/Th2) has shifted¹²
- 3. Detoxification and Biotransformation**
- Genetic profile of CYP 450 cytochromes — Tests for phase I detoxification polymorphisms to predict and prevent drug-drug and drug-food (or drug-supplement) interactions and to identify those who might not have the expected response to a medication that requires conversion in the body to an active compound; the test will detect both fast and slow metabolizers (e.g., CYP 2D6 and CYP 3A4 polymorphisms)
 - Functional detoxification panel of phase I (CYP 450) and phase II conjugation pathways — Assesses the body's detoxification capacity, using caffeine, acetaminophen, and salicylate, which challenge specific aspects of the detoxification process; these functional assessments also indicate, to a lesser degree of reliability, potential susceptibility to oxidative damage
 - Digestive stool analysis — Assesses enterohepatic circulation via levels of beta-glucuronidase (a deconjugating enzyme produced by pathogenic bacteria)
 - Assessment of exogenous toxins such as mold^{13, 14} and/or chemicals related to occupational and other exposures (e.g., chlordane, PCBs¹⁵) — Tests for chemicals increasingly associated with neuropsychiatric effects
 - 24-hour challenge test for heavy metals — If exposure is suspected¹⁶ based on occupation or the red blood cell mineral analysis

4. Oxidative/Reductive Homeodynamics

- Cellular energy panel — Evaluates organic acids that play a pivotal role in the generation of cellular energy; this test can reveal metabolic distress associated with generalized pain and fatigue, which may arise in response to toxic exposure, nutrient imbalances, digestive dysfunction and other causes; these organic acid metabolites primarily reflect carbohydrate metabolism, mitochondrial function, and oxidation of fatty acids that occurs during cellular respiration
- Functional detoxification panel (see above)
- Genetic profile of CYP 450 cytochromes (see above)
- 24-hour challenge test for heavy metals (see above)

5. Hormone and Neurotransmitter Regulation

a. Reproductive

- If a problem with male hormones is suspected, tests (at 8–9 AM) should begin with:
 - FSH
 - LH
 - Free testosterone
 - DHEA
 - DHEA-S
- If a problem with female hormones is suspected in menstruating woman, tests should include (at 8–9 AM, once during days 3–5 of the menstrual cycle—the follicular phase, and once during days 18–21—the luteal phase):
 - FSH
 - LH
 - Estradiol
 - Progesterone
 - 17-OH progesterone
 - DHEA and DHEA-S
 - Free testosteroneTesting hormones with a salivary female hormone profile will give much more data (about 11 days of data) about progesterone and estrogen ratios¹⁷
- If a problem with female hormones is suspected in postmenopausal woman:
 - Estradiol
 - FSH
 - LH
 - Progesterone
 - DHEA
 - DHEA-S
 - Free testosterone
 - Adrenal saliva test (see above)

b. Thyroid

- If baseline thyroid assessment (including physical exam, history, and laboratory tests) is suspicious, further tests should include thyroid peroxidase antibodies, TSH antibodies, and body temperatures
- If a goiter or nodule is found on physical exam, thyroid ultrasound and referral for possible fine needle aspiration should be considered

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- c. Adrenal
 - If hypothalamic-pituitary-adrenal (HPA) axis is overactive (cortisol is elevated) based on ASI, signs, and symptoms:
 - 24-hour urinary free cortisol — Rules out Cushing's syndrome (see below if cushingoid appearance) and exogenous steroid use
 - Assessment for pain and hypoglycemia as other causes of hypercortisolism (aside from a hypercortisolemic/hypernoradrenergic affective disorder)
 - If HPA axis output is significantly underactive based on ASI, signs, and symptoms, ACTH stimulation test at 8 AM to rule out adrenal gland insufficiency (the baseline ACTH done at initial evaluation will probably be elevated)
 - If there is a cushingoid appearance on physical exam, refer for further evaluation, which will include:
 - Abdominal CT scan to rule out adrenal or ectopic tumor
 - 24-hour urinary free cortisol test
 - Pituitary MRI should be considered
 - If ACTH is subnormal or above normal, pituitary MRI with and without contrast
 - If pituitary insufficiency is suggested on any of the other hormonal axes (e.g., panhypopituitarism), pituitary MRI with and without contrast to rule out pituitary microadenoma (present in 2–5% of the population); assess for chronic infection, which can cause a variety of abnormal hypothalamic/pituitary dysfunctions
 - d. Glucoregulation
 - If a glucoregulation problem is indicated (e.g., elevated fasting glucose, fasting insulin, or indicators of metabolic syndrome):
 - Fasting and 1- and 2-hour postprandial (following a 75 g glucose load) insulin-glucose tolerance test
 - HgA1c if diabetes is suspected
 - If there is a problem with sympathetic/parasympathetic balance, heart rate variability test
 - e. Melatonin
 - For patients with sleep-onset insomnia or sleep phase delay (circadian rhythm disorders), salivary melatonin test
6. **Structural Integrity**
- Sleep study — Can be considered to rule out apnea, PLMS, and decreased REM latency and to assess delta sleep if symptoms warrant
 - Exercise type, frequency, and intensity
 - If there is a brain injury, EEG brain mapping; neurofeedback and rehabilitation services should be considered
 - Sleep conditions (bedding, lighting, noise, temperature, snoring spouse, barking dogs, etc.)
 - If chronic pain syndrome, chiropractic evaluation, orthopedic evaluation, physical medicine consultation, and evaluation of job ergonomics should be considered
7. **Psychological and Spiritual Equilibrium**
- Beck Depression Inventory
 - Beck Anxiety Inventory
 - Yale Brown Obsessive Compulsive Scale
 - ADD testing (subjective questionnaire or continuous performance testing such as Test of Variables of Attention, or TOVA)

- Assessment should include:
 - Sources of learned helplessness, social defeat, and trauma
 - Marital satisfaction
 - Job satisfaction
 - Social and job skill deficits
 - Role changes
 - Losses
 - Current stresses
 - Depth psychological issues — Complexes that develop as a result of recurrently experienced trauma, are associated with ineffective stereotypic cognitive-emotional-behavioral repertoires, and are resistant to logical examination and behavior change

B — Clinical Interventions

Types of Depression: HPA Axis Connections

Before we begin our discussion of clinical interventions organized by areas of the Functional Medicine Matrix, there is an overarching issue that has important treatment implications. Two subcategories of depression may exist that are differentiated by the type of dysregulation of the stress response system (SRS), with differences in cortisol and norepinephrine (noradrenaline) output, cortical function, lateralization of pathology, and attendant differences in clinical phenomenology.¹⁸ These 2 subtypes of depressive disorder are *melancholic depression* and so-called *atypical depression* (which, depending on the particular clinical setting, is often more common than the classic melancholic depression). Individual dysregulation may occur anywhere on a spectrum that spans a hypercortisolemic/hypernoradrenergic state (melancholic depression) to a hypocortisolemic/hyponoradrenergic state (atypical depression). In a given individual, there are both state and trait aspects of this dysregulation, and so measures will vary over time, circumstances, and the chronicity of stress. Nevertheless, it is worth understanding the different poles of the spectrum, as it can expand our awareness of both the psychology and the physiology of depression. Table 7.3 shows some of the common characteristics of these 2 types of depression.

Table 7.3—Two DSM-IV Subtypes of Depression

	Atypical Depression	Melancholic Depression
Gender Predominance	F > M	M ≥ F
Age of Onset	Adolescence	Adulthood
Sleep	Increased	Decreased
Appetite/Body Fat	Increased	Decreased
Immunity	Vulnerable to inflammation	Vulnerable to infection
Diurnal Mood/Energy Variations	PM worse	AM worse
Reactivity to Environment	Yes	No
Energy/Locus Ceruleus Activity	Psychomotor retardation, reduced central norepinephrine	Psychomotor agitation, increased central norepinephrine
Heritability	Yes	Yes
HPA Axis Feedback	Excessive negative feedback and HPA axis downregulation	Excessive positive feedback and HPA axis upregulation
Laterality in Prefrontal Cortex	Reduced right prefrontal cortex activity	Reduced left prefrontal cortex activity

Melancholic depression — The classic type of depression is generally episodic, more common in males than females, and characterized by very severe symptoms. This depression is manifested by an intensely sad and hopeless mood and is accompanied by insomnia (particularly in the middle and later parts of the night), weight loss, a diurnal variation in which the depression is most severe in the morning hours, complete loss of pleasure or ability to anticipate pleasure (including sexual), impaired concentration, agitation, and suicidal preoccupation.¹⁹

This state of melancholic depression has been clearly associated with elevated central levels of norepinephrine and corticotropin-releasing hormone (CRH) and with hypercortisolemia.²⁰ Importantly, there is a failure to brake the stress response on at least 3 fronts:

- First, the ventral prefrontal cortex (PFC) fails in its function of inhibiting the amygdala and extinguishing conditioned fear responses, as well as to accurately predict whether a given situation will result in pain or pleasure. In fact, both imaging studies and postmortem studies consistently show a decrease in volume of the left subgenual PFC and overactivity of the left amygdala in this type of depression.²¹
- Second, a subset of cells in the paraventricular nucleus (the parvicellular division) appears to become autonomous of negative feedback, releasing a greater arginine vasopressin (AVP)-to-CRH ratio and sending activating signals to the locus ceruleus (LC). With continued stress, the ratio seems to increase. The specific AVP receptors are more responsive to chronic stimulatory input from cortisol, and this keeps the positive feedback loop active. CRH and AVP seem to act synergistically in activating the HPA.²²
- Third, cortical CRH receptors, which are part of a negative feedback loop at the level of both the PFC and the hippocampal cortex, are reduced in melancholic depression.²¹

Additionally, there is mounting evidence that the release of AVP occurs in the suprachiasmatic nucleus (SCN), which may be associated with seasonal depression and abnormalities of diurnal variation and sleep.²²

As a result of this sustained positive feedback response, in which the SRS inhibits the PFC and the left PFC fails to inhibit the core SRS, the patient remains in a hypercortisolemic, hypernoradrenergic loop that is often difficult to break unless both the antecedents and mediators of the condition are corrected. Some of the important issues to be addressed in this situation are social and work skills, cultural context, helplessness-inducing situations (e.g., social defeat, reduced response contingent reinforcement), hormonal dysregulation, nutritional deficiencies, and inflammation. Effective antidepressant treatments are known to increase cortical CRH receptors, reduce CRH and AVP levels, activate the PFC, increase hippocampal volume, and reduce cortisol. In some cases, electroconvulsive therapy may be necessary and effective.

Atypical depression — This type of depression has a higher prevalence in women, an earlier age of onset, higher rates of suicidal thoughts and attempts, and associated psychiatric comorbidities (panic disorder, drug dependence, disability, social phobia, childhood neglect, personality disorders, bipolar type II disorder, and sexual abuse). These patients exhibit a reversed diurnal variation in mood and energy, with worsening as the day goes on. Key symptoms that help differentiate the atypical patient from the melancholic are hypersomnia and hyperphagia,²³ possibly due to the loss of CRH inhibition of appetite.²⁴

In atypical depression, mood is generally temporarily responsive to environmental stimuli, but the person experiences a sense of inner emptiness that is pervasive. The loss of pleasure (anhedonia) of the atypical depressive is expressed as a difficulty anticipating pleasure (anticipatory anhedonia), but pleasure is experienced in real time (perhaps tied to the dysfunction of the ventromedial PFC, which, when functioning normally, helps one accurately anticipate whether an activity or situation will be rewarding or painful). Rather than experiencing the psychomotor agitation of the melancholic, the person with atypical depression experiences a great deal of fatigue, often referred to as leaden paralysis. Atypical depression is associated with chronic fatigue syndrome and fibromyalgia; however, the 3 conditions are distinct.

Neurophysiologically, it is generally thought that, unlike the melancholic, the atypical depressive exhibits a *lateralized*, centrally mediated (right PFC and amygdala) downregulation of the HPA axis and a central CRH deficiency. According to Gold²⁵ and the findings of the national comorbidity survey,²³ the genesis of this form of depression may have its origins in relational difficulties such as neglect and abandonment at an early age, consistent with studies by John Bowlby and René Spitz (anaclitic depression) in the 1940s. According to Schore, “a history of cumulative relational trauma (misattunement between mother and infant), or of frank abuse and neglect, represents a growth-inhibiting environment for the maturation of the right brain.”²⁶ The insecurely (abused, neglected) attached infant’s stressful experiences with a caregiver who commonly initiates but poorly repairs intense, long-lasting dysregulated states are incorporated into right-brain, long-term, autobiographical memory.²⁷ The implication here is that the common atypical depressive disorder and its comorbidities, which are rampant in our society, are the result, in part, of the early psychosocial environment of the mother-child interaction, which first causes a right-sided (?PFC) overactivity and actual suppression of the HPA axis and SRS. This lateralization is opposite to that found in melancholic depression.

Treatment implications — Unfortunately, most studies to date have not parsed out these different subpopulations, and there remains some skepticism about the validity of the concept. There is some evidence that atypical depression is less responsive to tricyclics²⁸ and that melancholic depression is more responsive to them. A consensus has emerged that atypical depression responds better to monoamine oxidase inhibitors (MAOIs, e.g., phenelzine and tranylcypromine).^{29, 30} However, with the advent of the SSRIs, the use of MAOIs declined precipitously, as SSRIs were found to be effective in this group of patients. Additionally, MAOIs often require a tyramine-free diet to prevent hypertensive reactions. The newer transdermal selegiline eliminates this problem at the lowest doses. (See *The Third Generation of Antidepressants* in Chapter 4.) It may retain superior efficacy in atypical depression, although this has not been proven.

Psychotherapeutically, based on the differences cited about etiology above, one would suspect that patients with atypical depression are somehow more vulnerable to the quality of the therapeutic relationship (and any misattunements that might develop) and have a greater need for emotional validation, while the melancholic depressives are more likely to benefit from a cognitive-behavioral/structural approach geared to the current situational triggers and rehabilitation. This conforms to the author’s clinical experience. However, much more research is needed on these and other important topics. For example, there is scant research on inhibitors of cortisol production (e.g., ketoconazole) and the use of cortisol for melancholic and atypical depression, respectively, although there are some preliminary encouraging results.

Clinical Pearl:

I use a mnemonic to organize my thinking around the Functional Medicine Matrix and to be more confident that I am not missing something important:

PONG DIED

- | | |
|-----------------------------|---|
| P = psychosocial | D = digestion |
| O = oxidative stress | I = immune/infectious and inflammatory |
| N = nutrition | E = endocrine |
| G = genomics | D = detoxification |

Although not included in the PONG DIED mnemonic, voluntary physical activity is as effective in mild to moderate depression as medication and results in an increase in brain-derived neurotrophic factor (BDNF) in the hippocampus in animals.³¹ *Regular exercise must be part of any treatment plan for depression, unless patients are hypothyroid initially or have some other limitation.*

Clinical Management Using the Functional Medicine Matrix

1. **Psychosocial** — As documented in the previous chapters, the best researched psychosocial treatments for mood disorders are cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT). In mild to moderate depression, the cognitive aspect of CBT is the most helpful, while in severe depression, the behavioral aspect is most helpful and the cognitive aspect is of little use (probably due to regional cortical hypometabolism resulting in cognitive inflexibility and impaired executive functions). Compared with CBT, there are fewer studies on IPT, but studies have also found it to be helpful and a good adjunct to other treatments. A newer treatment approach called interpersonal and social rhythms therapy (IPSRT) attempts to regulate daily activities, such as sleep, exercise, and eating patterns, as well as personal relationships, in order to achieve stability; IPSRT has been shown to be effective in management of bipolar disorder.³²

Clinical Pearl:

Long-term compliance with prescriptive treatments—whether medicinal, dietary, hormonal, or lifestyle—is a well-known problem. Taking a depth psychological approach to these problems can help identify whether psychological complexes (clusters of unconscious feelings and beliefs, detectable indirectly through behavior that is puzzling, illogical, and hard to account for) are preventing logical approaches to compliance problems from being effective. We all have these “complexes,” which are behavioral, cognitive, emotional, unconscious perspectives that are usually developed in childhood around some type of repeated trauma or stress. Most individuals are not aware either of their complexes or how their lives may be affected by these patterns. But by uncovering links to these attitudes, patients are often freed to control their own behavior and to partner in their health. For an example, see *Case Study—Tamika* in Chapter 8.

2. **Oxidative Stress** — Oxidative stress is frequently associated with immune, inflammatory, detoxification, and lifestyle factors. Once the presence of oxidative stress has been verified, clinicians must help patients address both the causes and the effects. The first step is to identify the sources of oxidative stress in the patient’s life, and then develop strategies for reducing or eliminating them. Next, ensuring the presence of sufficient antioxidants will be a key therapeutic strategy. Antioxidant load can be increased by the use of whole organic foods and freshly made vegetable and fruit juices; however, depending upon the degree of stress and the ability of the patient to make dietary changes, it may be necessary to use supplementation (e.g., lipoic acid, zinc, selenium, coenzyme Q10³³). Reducing intake of simple sugars will also be helpful because there is good evidence that hyperglycemia-generated oxidative stress is at least partially responsible for the development of insulin resistance.³⁴ Ultimately, chronic and excessive oxidative stress can cause damage to mitochondrial function, resulting in impaired energy in a variety of tissues, including the brain.
3. **Nutrition and Digestion** — Any nutritional deficiencies identified during testing should be remediated through a combination of foods and supplements (unless there are problems with digestion or absorption that also need to be remedied, such as SIBO). In the individual who is vulnerable to depression or nonresponsive to medication, nutrient deficiencies (e.g., vitamins B1, B6, and B12, folate, iodine, zinc, copper, magnesium, iron) can affect normal neurochemical function of the nervous system.³⁵

As discussed in previous chapters, high-dose folic acid (5–50 mg/d), along with adequate vitamin B12 supplementation, can, in and of itself, be a treatment for depression. In addition, folic acid can augment response to medication and—surprisingly—reduce side effects. B12 can be used sublingually (2500–5000 µg), or intramuscular B12 can be used if there is evidence of decreased B12 function (low functional intracellular assay result, higher than the mean MCV with or without anemia). Intramuscular B12 (methylcobalamin

1000 µg/cc, IM) should be given 3 times per week for 1 month, then once per week for 2 months, then the patient should go back to sublingual, unless there is reason to suspect continued absorption problems. Dosage frequency can be adjusted upwards if patients find it useful or downwards if the rare patient finds it overstimulating (in that case, dosage and frequency might have to be reduced). There are reports of high levels of folic acid inducing seizure; while I have never seen this clinically, it is something to be aware of.

Disturbances at the level of digestion and absorption should be assessed and treated using the help of a nutritionist, the 4R program (Remove, Replace, Reinoculate, Repair—discussed in the *Textbook of Functional Medicine*³⁶), and other approaches indicated by the full patient assessment.

IBS is often associated with depression,³⁷ and many patients with depression have a variety of gastrointestinal complaints even if they don't fulfill the criteria for IBS. Assessing delayed food allergies via IgG testing and correction of gastrointestinal imbalances via the 4R program have, in my experience, eliminated more than 90% of these complaints. A secondary but not unimportant benefit is improved immune function and reduced inflammatory burden, both of which are thought to be significant triggers and mediators on a neurochemical level in depressive disorders. Certain methods of hypnosis have been quite helpful in patients with IBS.³⁸⁻⁴⁰

SIBO is a common condition that is strongly associated with IBS,^{41, 42} and it often underlies chronic symptoms of maldigestion and malabsorption, including bloating, gas, constipation/diarrhea, irregularity, and abdominal pain. Without proper detection and treatment, SIBO can gradually lead to nutrient deficiency or insufficiency due to altered gastrointestinal function, which can increase vulnerability to depression.⁴¹

Clinical Pearl:

A patient who had depression and persistent nutritional deficiencies demonstrated on blood tests and whose blood levels did not correct with diet and supplements was found to have belching, constipation, and bloating after meals. A breath test indicated significant SIBO, which was treated with several cycles of rifaximin, 2 weeks on and 2 weeks off, along with an antifungal and probiotic support. After several months, his breath test, blood tests, energy, and mood normalized. In order to eliminate his constipation, which is often a cause of SIBO, it was critical to address the pancreatic insufficiency demonstrated on his stool test, which revealed markedly reduced pancreatic elastase, a marker of impaired ability of the pancreas to produce digestive enzymes. Following correction of the SIBO, we were able to correct his nutritional deficiencies and eliminate one of his psychotropic medications. This resulted in less sedation and a reduced medication burden, as well as a probable long-term improvement in his overall health.

As individuals age, or if they are on H2 receptor antagonists (e.g., omeprazole), the functioning of the parietal cells in the stomach deteriorates, resulting in reduced production of hydrochloric acid (stomach acid).^{43, 44} This has multiple consequences, including impaired digestion of proteins and increased risk of constipation and SIBO. Additionally, reduced absorption of vitamin B12 due to impaired release of intrinsic factor can occur.

- 4. Genomics** — A thorough family history will often reveal many relatives with affective disorders or affective disorder-related illness, either psychiatric or medical (e.g., heart disease, diabetes). While a strong family history makes one suspicious of a genetic vulnerability to affective disorder, it does not prove genetic vulnerability because early rearing experiences in these populations are more likely to be abnormal. However, a family history of completed suicide or a violent suicide attempt should alert the clinician to a higher risk of biological vulnerability and suicide, since violent suicide attempts may be correlated with abnormalities

in cerebrospinal fluid 5-HIAA, a marker of serotonergic function.^{45, 46} In such cases, a very careful assessment of suicide risk is critical; if suicide ideation is present, one would do well to consider the immediate use of lithium, which is the only medication proven to reduce the risk of suicide.^{47, 48} Lithium can be used temporarily to safeguard the patient and augment antidepressant response while the other aspects of the Functional Medicine Matrix are assessed and treated.

Clinical Pearl:

Disturbances in normal gastrointestinal flora, such as overgrowth of yeast, are common in patients with depression, particularly those with atypical depression, because of the tendency to overeat and crave carbohydrates. A recent case of a 28-year-old attorney was striking. She came to me with intense anxiety and panic attacks, as well as a sense of hopelessness and helplessness. A stool test detected the presence of *Strongyloides*, which was treated successfully with ivermectin, 200 µg/kg/d. While the standard treatment recommendation is for 2 days, an extended 7-day course was prescribed by her internist. Additional triggers of her anxious depression involved job difficulties, recurrent illness in her young child, and living in a high-mold environment with her widowed mother-in-law while her home was being built. Each of these factors needed to be addressed. However, there was a quite surprising and dramatic improvement (70%, by the patient's estimate) with treatment of *Strongyloides*, including elimination of her panic (but not her anticipatory anxiety), overall reduced anxiety, elimination of depression, and successful discontinuation of antianxiety and antidepressant medication. Since there was no evidence of disseminated infection, the remarkable improvement was most likely due to hematologic, immune, and nutritional normalization.

In all likelihood, the genetic component of vulnerability to depression is the result of multiple genes of small effect working in tandem with antecedents and triggers (e.g., developmental, environmental, lifestyle, psychosocial, spiritual, cultural influences). A brief review of the functions of these genes does support the central concept advanced in this monograph: *that depression is a disorder which affects and is affected by the entire person and all of the body's major subsystems*. While no single genetic vulnerability fully accounts for the expression of the depressive phenotype and hundreds of gene candidates have been studied, there is statistically significant evidence for 6 susceptibility genes: APOE, DRD4, GNB3, MTHFR, SLC6A3, and SLC6A4.⁴⁹

- Simply stated, APOE is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. APOE has been studied for its role in several biological processes not directly related to lipoprotein transport, including Alzheimer's disease, immunoregulation, and cognition.
- The DRD4 gene is associated with the dopamine receptor. Mutations in this gene have been associated with various behavioral phenotypes, including autonomic nervous system dysfunction, ADD, and the personality trait of novelty seeking, as well as depression.
- The COMT gene codes for the enzyme that helps degrade intrasynaptic catecholamines (e.g., dopamine, catechol-estrogens). Individuals who are homozygous for the COMT Val allele have diminished prefrontal dopaminergic levels and impaired executive function.⁵⁰ Adequate amounts of methyl donors such as folic acid (1–5 mg/d) and S-adenosylmethionine (S-AdoMet, typically 200–400 mg, 3 times per day on an empty stomach) can enable these enzymes to function at their optimal levels.
- GNB3 (guanine nucleotide-binding proteins) is a gene that codes for the beta subunit of G proteins. G proteins integrate signals between receptors and effector proteins within the cell. Beta subunits are important regulators of certain signal transduction receptors and effectors. A single nucleotide polymorphism (SNP) in this gene (C825T) is associated with essential hypertension and obesity, as well as depression.

- The C677T MTHFR polymorphism is more common in patients with affective disorders and heart disease.^{51, 52} Particularly in those heterozygous for the SNP, impaired neurotransmitter regulation can occur, often manifested in laboratory testing by elevated homocysteine (except in those with heavy metal toxicity). This is easily corrected by use of 5-methyltetrahydrofolate (dosage should be assessed by measurement of fasting homocysteine level) with B12. Such treatments should be instituted on a lifelong basis and consideration should be given to testing other family members.
- SLC6A4 and SLC6A3 code for the reuptake pump or transporter for serotonin and dopamine, respectively. These genetic variants can influence transporter function by various mechanisms, including substrate affinities, transport velocity, transporter expression levels (density), extracellular membrane expression, trafficking and turnover, and neurotransmitter release. It is increasingly apparent that genetic variants of monoamine transporters also contribute to individual differences in behavior and neuropsychiatric disorders.⁵³

Clinical Pearl:

Clinically, I have found that patients who are homozygous for the COMT polymorphism often have unusually high degrees of anxiety associated with their depression. Those who are not responsive to folate or SAMe frequently benefit from low-dose neuroleptics (such as quetiapine, 25 mg at bedtime, or even lower) in the antipsychotic category.

Clinical Pearl:

Polymorphisms of CYP 450 systems (e.g., 3A4 and 2D6) can be tested for and should be used to predict and prevent drug interactions and sensitivities. This is particularly relevant today, when many patients are on multiple medications.

5. **Immune Surveillance/Inflammation/Infection** — The association of depression with inflammation discussed in earlier chapters of this monograph suggests that the nervous, endocrine, and immune systems are linked as both triggers and mediating pathways. The clinician treating depression needs to learn to detect and assess triggers of the inflammatory immune response via history and physical exam. Triggers can include psychosocial stressors (known to dysregulate immune response), foods, respiratory allergens (e.g., pollen, dust, molds), environmental toxins (e.g., chemicals such as PCBs and chlordane, heavy metals), and infections (e.g., chronic sinus infections, silent root-canal infections, tick-borne diseases).

The treatment will normally include removing as many triggers and mediators of immune dysregulation as possible (e.g., sensitive foods, allergens, infections), improving vitamin D status, recommending the use of appropriate antioxidants, providing adrenal support (e.g., pantothenic acid, vitamin C, zinc, copper, ginseng, *Rhodiola*, meditation, psychosocial intervention), and selecting from among many other potential therapies, such as:

- Food extracts (e.g., *Cordyceps* to improve NK cell activity)
- Anti-inflammatory supplements (e.g., curcumin)
- Anti-inflammatory medications (including physiological, not pharmacological, doses of hydrocortisone, if indicated)
- Antihistamines (though these can worsen depression)

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- Antifungals (these can suppress adrenal corticosteroid output, which can be beneficial in melancholic hypercortisolemic depression, but can worsen the atypical hypocortisolemic variety)
- Antibiotics (both natural and pharmaceutical)

A common complaint of people with depression is “brain fog”; treatment of pertinent immune, inflammatory, and infectious factors frequently eliminates this completely, although improving noradrenergic/adrenergic status via supplements such as tyrosine/phenylalanine or stimulant medications can be required. Other inflammatory symptoms such as arthritis, fibromyalgia tender points, fatigue, weight gain, and skin problems may improve, as well.

6. **Endocrine** — These disorders routinely present with symptoms of depression, including disturbances in the autonomic, thyroid, adrenal, reproductive, glucoregulatory, or chronobiological axes. These disturbances may be the primary cause of depression or, more often, the secondary result of a variety of factors, including chronic stress, chronic illness (including cancer), malnourishment, chronic inflammation, toxic burdens, or infectious processes. Whether primary or secondary, these disturbances must be addressed (unless treatment is contraindicated due to the primary diagnosis) in order to help the depressed individual recover full and vital function with as little medication as possible. The general approach can be supportive (e.g., reducing stress; treating inflammation; improving detoxification, digestion, and diet; supplementing with amino acids or minerals), or it can also involve hormone supplementation. The decision about which approach to take will depend on the urgency for recovery and the orientation of both patient and physician. If hormonal supplementation is chosen, appropriate supportive measures should be instituted at the same time.

The various endocrine axes interact on many levels in ways that are not yet fully understood. (See Chapter 6, *Mechanisms and Interconnections within the Functional Medicine Matrix Model*.) With the complexity of these relationships and interactions in mind, let’s look now at treating dysfunctions in the individual hormonal axes involved in the affective disorders.

- a. **Thyroid and adrenal** — When treating the patient with hypothyroidism (much more common in affective disorders than hyperthyroidism), one must consider several issues. Adrenal axis function must first be assessed to be certain that cortisol output is sufficient for the patient to tolerate introduction of thyroid hormone, if needed. If thyroid hormone is introduced in the presence of significant hypocortisolism, the patient can experience overactivation (e.g., anxiety and agitation), despite needing thyroid hormone.

If adrenal axis output is abnormal, then the source of the dysfunction must be determined; among the many possible problems to look for are adrenal gland insufficiency, pituitary insufficiency, hypothalamic insufficiency, brain stem or limbic dysregulation, or psychosocial-spiritual dysfunction (e.g., a misattunement in a major relationship).

- If the ASI result indicates reduced cortisol output, the first step is usually to determine that the adrenal gland itself is functioning and responding appropriately; so an ACTH stimulation test should be done. In practice, the results of this test are usually—but not always—normal.
- Moving up the adrenal axis, pituitary function should be assessed. Is the ACTH output normal, low, or high? If it is low, one would wonder about a pituitary microadenoma (present in about 3-5% of the population), particularly in the face of low levels of other pituitary hormones such as FHS and LH; abnormalities in many other hormonal axes could be relevant as well. High ACTH output is suggestive of an adrenal gland malfunction, but can be generated by pituitary or higher center problems and even certain tumors in 12% to 17% of Cushing’s syndrome cases. In addition to small cell lung carcinoma, the most common causes of ectopic ACTH production are bronchial carcinoids, thymic tumors, islet cell tumor of the pancreas, medullary thyroid carcinomas, and pheochromocytomas.⁵⁴

Clinical Discussion: Experiences in Assessment and Treatment

- If pituitary function appears normal, then we can move up the ladder of the adrenal axis to consider the role of the hypothalamus. It is worth noting that infection, inflammation, and immune activation (via, for example, chronic mold exposure, chronic sinusitis, and tick-borne diseases) do alter HPA function at the hypothalamic level and should be investigated as part of this process.
- Next, we should consider the limbic (e.g., amygdala, hippocampus) and brain stem (e.g., the LC, a brain stem nucleus involved in panic, and the solitary nucleus, a brain stem nucleus involved in the regulation of anxiety), areas involved in the emotional disorders. The determination of the role of these centers in the genesis of adrenal axis dysfunction is generally based on history. A temporal lobe seizure disorder (e.g., partial complex seizures without loss of consciousness) or post-traumatic stress disorder would involve these pathways and structures and lead to HPA dysregulation over time.
- Finally, an assessment of early life relationships, looking for misattunement (as well as neglect and abuse) between the mother or primary caregiver and the patient will help the clinician to know whether the origin of the hypocortisolism is based in relational misattunement, impaired development of a sense of identity and self, and attendant right hemispheric developmental disorder.⁵⁵

The supportive approach to adrenal dysfunction that is not due to a tumor, a microadenoma, autoimmune disease, or Cushing's or Addison's disease, involves the use of meditation, stress-reduction techniques, elimination of hypoglycemic stress and physical pain, adaptogens (e.g., *Cordyceps*, ashwagandha, ginseng), vitamin C, pantothenic acid, mineral repletion (particularly zinc and/or copper, if deficient), moderate exercise, and encouragement of fun activities, as well as psychotherapy geared toward psychosocial/spiritual issues. Some practitioners use extracts of adrenal tissue with success, although I have been reluctant because of content and quality control issues.

If the supportive measures do not restore adrenal function sufficiently so that thyroid hormone can be tolerated, the use of hydrocortisone in physiological doses of approximately 20 mg/d can be considered. In my experience, many patients with chronic depression that is characterized by frequent relapses and partial remissions in conjunction with demonstrated reduced output of the adrenal axis benefit from use of hydrocortisone. In these patients, energy seems to improve significantly and the increased ability to handle even minor daily stresses is remarkable. (*Safe Uses of Cortisol* by William McK. Jeffries⁵⁶ is an excellent reference for those interested in this option.) Patients who elect this option need to be instructed to wear a medical alert bracelet, to take the medicine only as prescribed, and to observe for any signs of excessive hydrocortisone usage such as fluid retention, weight gain, or craving for sweets. Some patients require less than the usual dose, so it is beneficial to start at 10 mg/d. The typical patient would take 10 mg upon waking, 5 mg at 11 AM, and 5 mg at 3 PM, with a fat-containing snack at each dose. In the event of stress, illness, or surgery, the dose should be increased by 25% to 100% for the duration of the stress or illness. The use of hydrocortisone should normally be limited to a period of 6 months to 1 year, at which point the medication is tapered off in a gradual manner following the standard endocrine procedure for corticosteroids.⁵⁷ Tapering off hydrocortisone is not problematic, as long as the supportive measures mentioned above are incorporated into the patient's life.

Once the adrenal issues are addressed, the clinician needs to determine whether to use T4, T3, or a combination of the two. This is best determined by looking at the relative levels of free T4 and free T3. It is not uncommon to see patients who have normal, midrange, or high-normal free T4 with low-normal free T3. In these cases, the difficulty is in the conversion of T4 to T3 in the liver (which can be due to several factors), and use of T3 is preferable. In treatment-resistant depression, relatively high doses of T3 can be used, such as 25 µg/d for a week and then 25 µg twice daily thereafter, along with initiation of an antidepressant.⁵⁸ Doses this high usually result in high blood levels of free T3 and suppressed TSH, without clinical signs of hyperthyroidism. When one is not working with such large doses, it is best to follow the clinical picture (including temperatures and the relaxation phase of deep tendon reflexes, as well as other signs and symptoms and lab tests) to determine appropriate doses.

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Patients must take thyroid hormone in a consistent manner and on an empty stomach away from supplements, all food, and other medications. Adjustment of thyroid doses should always be followed by the standard thyroid panel about 6 weeks later, done in the morning if one wants to determine trough levels of free T3 or about 4–6 hours after T3 supplementation if one wants to determine peak levels of free T3. Excessive doses of thyroid hormone resulting in suppressed TSH may be associated with osteoporosis, and so the cost-benefit balance of such an approach must be considered in each patient. Weight-bearing exercise, regular bone scans, optimal calcium and vitamin D status, reduction of inflammation, and perhaps bisphosphonates and/or vitamin D analogs may help to temper the risk if the patient does need suppressive therapy. Thyroid antibodies also should be tested, including thyroid peroxidase antibodies and, if the patient appears hyperthyroid, TSH antibodies. Patients with Hashimoto's thyroiditis may require closer monitoring and dosage adjustments, as well as supplementation with selenium and attention to adrenal function.

The clinician needs to be aware that a consensus has been developing since the 2002 NHANES study⁵⁹ that the standard reference range for TSH is inappropriate. For patients with affective disorders, it is generally best to keep TSH levels between 0.5 and 2.0 mIU/L.^{60, 61}

- b. Reproductive hormones — Deficiencies in reproductive hormones can arise from several sources, such as nutrition (e.g., low zinc is associated with treatment-resistant depression,⁶² inflammatory states,⁶³ and low testosterone production⁶⁴), stress, toxins (e.g., marijuana reduces testosterone production), pituitary microadenoma, total oophorectomy, or genetic problems (e.g., Klinefelter's syndrome). These disturbances (in both men and women) are clearly associated with depression as both cause (less often) and contributors to treatment resistance. Of course, adrenal deficiency in itself, as well as deficient gonadal output, can be contributory to low reproductive hormones. In males and females, measurement of FSH, LH, zinc, free testosterone (taken as baseline in the morning and on 3 occasions at the same lab to establish low testosterone), DHEA, DHEA-S (preferably via an ASI and blood), and estradiol should be taken.

In older males, PSA and prostate exam are used as part of the baseline measures. If established, replacement of appropriate hormones can be very helpful with mood, cognition, muscle strength, sexual function, and self-esteem. Excessive doses can cause increased hematocrit, sleep apnea, irritability, acne, and male pattern hair growth; therefore, regular monitoring of blood levels of free testosterone (4–6 hours after morning application of gel or patch) is necessary.

The clinician should be alert to certain genetic enzymatic deficiencies in women; for example, 17- and 21-hydroxylase deficiencies are more common in Ashkenazic women of eastern European ancestry. These deficiencies can be associated with reduced cortisol output (and, therefore, intense fatigue, difficulty handling stress, and depression), increased signs of virilization, infertility (polycystic ovaries), metabolic syndrome, and so forth.

Peri- and postmenopausal women with depression have been shown to benefit from use of the estradiol patch,⁶⁵⁻⁶⁷ but not oral estradiol or synthetic estrogens. Use of the patch can be considered in some patients, taking into consideration the risks and benefits of using exogenous hormones. If used, many gynecologists prefer to add a small dose of progesterone (e.g., 50–100 mg at bedtime) so as to avoid the risks of using unopposed estrogen. The clinician and patient must work with the patient's gynecologist or other primary care provider to assure appropriate medical follow-up.

In the case of depression associated with the menstrual cycle (premenstrual dysphoric disorder or PMDD), the clinician should first document mood and relevant symptoms for 3 months, while collecting hormonal data (as described above) to document the diagnosis. If indicated, based on the data collected, the use of bioidentical progesterone in the luteal phase of the menstrual cycle can be quite

helpful, with or without an estrogen patch in place. Again, if using this approach, clinician and patient must work with the patient's primary care provider to assure appropriate medical follow-up.

Generally speaking, it is helpful for the clinician to correct as many adrenal hormones as possible by intervening as high up in the adrenal cascade as possible. Since cholesterol is the mother molecule for all adrenal steroid hormones, many people on statin drugs can develop subtle adrenal insufficiency with reductions in pregnenolone, DHEA/DHEA-S, cortisol, testosterone, and estrogen levels. Cholesterol is converted to pregnenolone, which then is metabolized along multiple pathways in the adrenal gland, and so use of pregnenolone can be quite effective. If used, then repeat testing of downstream hormones (DHEA, testosterone, estradiol) should be performed to ensure that levels of these hormones are within normal limits. There have been both positive and negative studies on the use of high-dose DHEA (e.g., 500 mg/d) in treatment of depression⁶⁸⁻⁷⁰; however, use of pharmacological doses of reproductive hormones entails unknown risks. In general, whether one is supplementing with DHEA, testosterone, estrogen, or progesterone, using bioidentical hormones to establish normal physiological levels is the most prudent approach. When testing for DHEA and testosterone levels after supplementation, such testing should be done about 4–6 hours after administration of the hormone. Oral hormones should be taken with a fat-containing snack since the steroid hormones are lipid soluble.

A proper balance between 2-hydroxy estrone and 16-alpha-hydroxy estrone is important for optimal health. Flaxseed and soy products (isoflavones),⁷¹ cruciferous vegetables (indole-3-carbinol⁷²), increased lean body mass,^{73,74} and omega-3 fatty acids⁷⁵ are interventions that may reduce the risk of estrogen-dependent disease by favorably modifying this ratio. Practitioners should closely monitor the physiological impact of these and other treatments (including the use of the estrogen patch in perimenopausal and postmenopausal women with depression), particularly in those women who are thought to need additional estrogen as part of their antidepressant regimen and who may have risk factors for estrogen-sensitive diseases. A cost-benefit analysis must be made in such cases.

- c. Glucoregulation — Maintaining stable glucose levels appears to be important in management of mood. Treating insulin resistance and type 2 diabetes can show multiple positive results, including improvement in metabolic parameters, the mood disorder, energy, markers of inflammation, and self-esteem. The focus should be on adjusting the patient's diet to (a) eliminate high-glycemic-index foods, (b) provide the appropriate balance of protein, fat, and complex carbohydrates, and (c) moderate caloric intake. Meals should be more heavily loaded (higher caloric content) toward the first two thirds of the day, unless the patient is taking 5–6 small meals per day. In addition, supplementing with plant sterols and appropriate minerals such as chromium (200 µg, up to 3 times per day, depending on red blood cell chromium levels) and R-lipoic acid (200 mg, 3 times per day) and instituting a program of regular, moderate exercise are all very useful interventions. Eliminating any sensitive foods from the patient's diet and correcting any gastrointestinal disorders are also important steps to take. Generally, insulin resistance can be normalized using this approach within 3 to 6 months; it has been effective with over 90% of the patients in my clinic whose conditions warranted this type of intervention. If significant weight loss is expected, it is important that the gastrointestinal and liver detoxification pathways be supported using lipoic acid, milk thistle, and a multi-mineral supplement (or one of a variety of medical food liver/gut support products) because weight loss is accompanied by release of fat-soluble toxins and hormones from adipocytes. Using a behavioral support program to maintain these lifestyle changes is also important. This can involve, for example, periodic follow-up phone calls to the patient, routine check-in appointments, and/or a behavior-modification program with built-in, agreed-upon punishments and rewards.
- d. Melatonin — Given that it is a hormone, melatonin should be used only if low or low-normal levels are detected. Melatonin dosage can range from 0.5 to 10 mg. I suggest measuring with salivary samples, then titrating to a dose that normalizes levels. It is important to recheck and make sure the dose is not

too high. Remember that supraphysiological doses of hormones put us in unknown and potentially dangerous territory.

7. **Detoxification** — Hepatic detoxification systems may affect brain function. Therefore, effective treatment of affective disorders must include assessment and treatment (if necessary) of phase I and II detoxification pathways, as well as dysbiosis. Although exhaustive clinical studies have yet to be performed, we have the biochemical and logical basis upon which to recommend interventions in order to help patients with evidence of chemical sensitivity or high exposures to toxic compounds.

It is important to realize that any change in the metabolic clearance of a drug—whether induced by an enzyme, another drug, or a food, herb, or supplement—can result in a change in steady-state concentration that will alter its effect.⁷⁶ Knowledge of CYP 450 interactions is essential whether one is treating with whole foods, pharmacology, or herbal supplements. In addition, if dysbiosis is present in the gastrointestinal tract, the conjugation reaction (glucuronidation) performed by the liver is undone by pathogenic bacteria in the intestinal tract, releasing toxins and hormones (e.g., estrogens) which are then available for reabsorption in the bloodstream and CNS, with attendant psychotropic effects.

Liver and gut support can reduce medication side effects, doses of medication, and toxicity and can affect the brain via hormonal and catecholamine pathways, as well as first-pass metabolism in the gut and the liver. Failure to address gut-liver alteration can result in continued dysfunction of hormonal and catecholamine metabolism, treatment resistance, unnecessary side effects, noncompliance, neurotoxicity, increased relapse rates, decreased remission rates, excessive medication doses, and drug-drug interactions.

Clinical Pearl:

Because nutritional modification of the CYP 450 and/or conjugation pathways has strong potential to change drug metabolism, practitioners should use caution and awareness when recommending such strategies in patients taking prescription medications or useful herbal supplements such as St. John's wort. St. John's wort can be recommended when patients express a preference for a natural approach, rather than a pharmaceutical one. Many studies have shown St. John's wort to be as effective in mild to moderate depression as antidepressant drugs.⁷⁷⁻⁷⁹ However, it's very important to prescribe a supplement whose quality and efficacy you can trust. The Web site www.consumerlab.com can be consulted to check on various products by name.

C — Practical Implications and Considerations

Many clinicians who do not have specialized training in psychology or psychiatry treat depressed patients. It is our hope that this monograph will provide information that can help improve their patient outcomes. However, because depression carries the risk of suicide and has such harmful effects on quality of life, it is critical to be alert to situations in which a referral to a specialist may be indicated for further evaluation or for treatment. I have had experiences in practice that have made me concerned that inadequate training and inadequate time allotted to patient evaluation and follow-up, particularly in the managed care setting, are leading to inappropriate prescribing practices and the inadvertent worsening of depression outcomes, including an increased risk of suicide.

There are several positive potential outcomes of integrating a functional medicine approach into the assessment and treatment of depression:

Clinical Discussion: Experiences in Assessment and Treatment

- Reliance on medication as the primary therapeutic option is no longer necessary; fewer medications may be needed (or even none), and those used will be more efficacious.
- There are many conditions that are comorbid with depression (as discussed extensively in this monograph), and the effects are often multidirectional: depression can worsen the course of other conditions, and other conditions can adversely affect the depressed patient's mood. Acting on multiple major problem areas simultaneously increases the likelihood of improving the depression, improving general well-being, and reducing comorbidities.
- Outcomes may be improved. For example, a study by Coppen⁸⁰ with 127 patients showed a significant improvement in response rate (94% vs. 61%, $p < 0.005$) for those on fluoxetine and folate vs. those on fluoxetine alone. Furthermore, the recovery rate increased from 47% (fluoxetine alone) to 73% with the addition of folate ($p < 0.06$). A recent meta-analysis of the association between low folate and depression confirms the finding.⁸¹
- Side effects may be reduced or avoided entirely. In that same Coppen study, adverse events severe enough to cause withdrawal from the trial and reports of side effects were both significantly lower in the folic acid group ($p < 0.05$).
- A reduced public health burden will result from the lessening of both mental and physical complaints.
- Clinician satisfaction can increase markedly with improved patient outcomes.
- The clinician who pays attention to both the mental and physical health of the patient avoids seeing the patient as *either* a psychological *or* a medical case—a most uncomfortable (and unrealistic) split.

Unfortunately, there are also obstacles to providing this kind of care.

- Most conventional practitioners are educated in an acute-care model, in which the thinking is linear and the goal is to control physiology, rather than a systems-oriented model, in which the goal is to manage multiple interacting factors to improve multiple affected processes.
- Managed care places a significant burden on practitioners, who may have less time for direct patient care and who may also be experiencing financial pressures from reduced reimbursement schedules. Functional medicine requires time—time to elicit the patient's story in depth, time to explore all the elements of dysfunction that are disturbing the patient's well being, and time to restore balance and function. And the short-term cost of both assessment and treatment can be significant if not reimbursed by a third-party payer. The need for studies to document the efficacy of the functional medicine model is urgent; research can drive policy change to support a paradigm shift in both delivery of care and reimbursement.
- Individuals and families, as well as clinicians, are under considerable time pressure. Americans work more hours per year than people in any other developed country, and the economic pressures (perceived and real) that drive this phenomenon are not likely to lessen. Time to exercise (sedentary occupations are now the norm), to eat together as a family, to prepare fresh, healthy, locally grown food, to participate in pleasurable activities, and to make friends and spend time with them is in short supply.
- Depression still carries a stigma. The clinician must engage the patient—via education about biology as well as the learned helplessness and social defeat models—in understanding that help can be provided, but only if all the necessary information for understanding the patient's condition is forthcoming. Despite public education, many patients need reassurance that being depressed is not a character flaw or a moral lapse. It is the result of complex interactions among genetics, biology, experiences, and the environment within which the patient lives.
- Depression itself reduces the inclination for self-care, which is an essential component of functional medicine.

Utilizing the functional medicine approach requires that you listen to the patient, collect a very detailed and comprehensive history, work in partnership with the patient to remove obstacles to self-care, and develop and use your relational/empathic, analytic, and critical thinking skills. There are no algorithms, no one-size-fits-all therapies.

Depression: Advancing the Treatment Paradigm

Each person must be evaluated as a unique individual, and the treatment plan must be tailored individually to address his/her particular issues. We have discussed many strategies that will help you meet these goals, but even this lengthy monograph is not exhaustive; each clinician must keep learning and integrating new knowledge on a regular basis to keep the model alive and growing.

Decisions are not made unilaterally in this model; they are discussed between patient and physician. Clinicians should take the time to explain the need for partnership in this approach. Patients are the experts on their own lives, while the doctor is the expert in medicine. Patients have a responsibility to provide honest, complete, and accurate information; they make the final decisions about their own treatment; they are accountable for following through with agreed-upon plans. They must keep scheduled appointments and prepare for appointments with prioritized questions, and they must be encouraged to contact the doctor with any concerns, change in plans, or information about side effects.

The practitioner's job as an agent of healing in the treatment process is to provide the most effective treatment possible for the patient's condition. Clinicians have a responsibility to be open-minded and communicative, to listen carefully and ask all relevant questions, to be reasonably accessible, to keep their knowledge scientifically and clinically current, to maintain confidentiality and professionalism, and to acknowledge areas beyond their capabilities and refer for second opinions as necessary.

In our next and final chapter, we will present several case histories that exemplify how a more comprehensive approach to assessment and treatment can help the clinician improve outcomes for patients with depression. I am certain that you will have many wonderful experiences as you begin to use this new approach with your patients!

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