Chapter 14
Psychiatric Diagnosis: Toward a Memetic–Epigenetic Multiaxial Model

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14.1 Psychiatric Diagnosis and Problems with DSM

In Chapter 1, I described the evolving model of mental illness as a result of epigenesis, the turning on and off of genes in interaction with environment. In Chapter 2, we examined how stress, newly introduced memes that interact with resident memes in the brain, causes changes in genes and brain structures. In the subsequent chapters, we examined the nature of memes as brain code and how culture as memetic pools affect mental health and illness. We saw that memes as neural connections are the actual agents of culture affecting genes and physiology. In this chapter, we will consider briefly the history of psychiatric diagnosis and then

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discuss what rational psychiatric diagnostic scheme should be in the light of gene × meme × environment interaction.

A widely accepted diagnostic scheme is the official diagnostic scheme of the American Psychiatric Association, *The Diagnostic and Statistical Manual of Mental Disorders (DSM)*. The fist DSM, published in 1952, was based on Adolf Meyer's psychobiology, a model that prominently posited the interaction among constitution, personality, and environment (Meyer and Winters, 1950). Psychiatric disorders were considered to be *reactions* of the personality in adapting to environmental demands. Both DSM I and DSM II (published in 1968) were based on the then prevailing etiologic theory – psychodynamics. DSM III, published in 1980, was a frank admission of the inadequacy of the psychodynamic model as it attempted to redefine psychiatric diagnoses as research questions rather than coherent entities. By adopting an "atheoretical" model, it dropped the psychodynamic view of etiology and the notion of neurosis, that there is a continuum of psychiatric problems or conflicts between the normal and the psychiatrically ill. It adopted, to a large measure, the "research criteria for psychiatric diagnosis" that was designed to choose "pure cultures" of major psychiatric disorders for genetic research (Feighner et al., 1972). DSM III and its direct successor, DSM IV (1994), classify major psychiatric syndromes into mutually exclusive categories (e.g., schizophrenia vs. schizoaffective disorder) presumably based on the notion of different genetic underpinnings. Though it claimed to be atheoretical, it thus implicitly adopted a biological/genetic model of psychiatric syndromes. Another outstanding feature of DSM III and IV is the multiaxial system of diagnosis – Axis I: Major psychiatric syndromes, Axis II: Personality disorders and developmental disorders, Axis III: Medical diseases, Axis IV: Stressors, Axis V: Global assessment of functioning (GAF). This system explicitly makes the important declaration that psychiatric syndromes and medical diseases coexist in a patient, and has made important contributions in avoiding the "either physical or all in the head" notion of a symptom.

DSM III and IV have helped foster psychiatric research by defining reliable populations for study. This fortuitously coincided with the rapid development in molecular biology and genetics, psychopharmacology, neuroimaging, and the completion of the Human Genome Project. If we can define a "pure culture" of a genetic syndrome, we are now in a position to understand its genetic underpinnings.

The multiaxial system of DSM III and IV, in addition to recognizing the coexistence of medical and psychiatric conditions, has also pioneered the notion that diagnosis is more than the listing of diseases but also includes the personality aspect of the patient, as well as the role of stress and the level of functioning. It is an attempt to diagnose the *patient*, not merely the disease.

On the negative side, the problems include: confusion concerning the categories and criteria for diagnosis, confusion concerning the distinction between Axis I and Axis II, and confusion concerning the nature and function of multiaxial diagnosis.

Confusion concerning categories: Any clinician attempting to use DSM III and IV realizes that the diagnostic criteria are arbitrary. While it is possible to assign a patient mechanically to one diagnosis or another, it often makes no clinical sense. We often realize that there are patients who almost meet the criteria, or meet most of

the criteria for more than one category. Examples include the differentiation between schizophrenia and schizoaffective disorder, making the diagnosis of borderline personality disorder, and classifying psychosis in a patient with the history of both schizophrenia and substance use. Genetic research of probands with the categorical diagnoses has shown that, in fact, these categories are *heterogeneous*, that many different genes may underlie the same category such as schizophrenia and bipolar disorder (Cheng et al., 2006; Prathikanti and Weinberger, 2005) and that one or a few genes may underlie many different categories such as bipolar disorder, schizoaffective disorder, and schizophrenia (Caspi et al., 2002, 2003; Craddock et al., 2006; Hamshere et al., 2005; Murphy et al., 2004). It seems clear that attempting to find the biological underpinnings of current categorical diagnoses is a wrong approach. The "biological underpinnings" have been shown to be for brain states and traits that may be associated with a variety of psychological/functional predispositions and deserving of a status independent of specific Axis I diagnosis.

Confusion concerning distinction between Axis I and Axis II: What is the distinction between a personality disorder and a major psychiatric disorder? Is schizophrenia not a developmental, personality disorder? Where does a borderline personality with a psychotic episode belong in this scheme? Genetic studies have also shown that there may be a continuum between personality disorder and a major psychiatric syndrome, e.g., borderline personality and bipolar disorder (Akiskal et al., 2003; Smith et al., 2004).

Confusion concerning the nature and function of multiaxial diagnosis: What is the multiaxial diagnosis the diagnosis of? Axes I and II are diagnostic categories with explicit criteria, Axis III is diagnosis without explicit criteria, Axis IV is a list of stressors, Axis V is a scale. Axes IV and V are, strictly speaking, not diagnoses at all. What is the overarching framework for this laundry list? What are the functions of Axes IV and V in a diagnostic scheme?

The problems of DSM III and IV are rooted in two major areas. One is that it is based on a conceptually faulty notion that psychiatric illnesses are categorical and discrete. Second is that the multiaxial system is a hodge podge of interesting and important areas to consider in making a diagnosis that lack conceptual rigor.

Discussing these problems with the current DSM, McHugh (McHugh, 2001, 1992, 2005; McHugh and Slavney, 1998) called for a rethinking of psychiatric diagnosis along the *perspectives* of disease, dimensions, behavior, and life story. He proposed that mental illnesses be considered in four, non-mutually exclusive clusters – (1) disease (e.g., schizophrenia), (2) psychological vulnerabilities (e.g., emotional stability), (3) behavior (e.g., alcoholism), and (4) distress evoked by events (e.g., grief).

Some (Genova, 2003) have called for "dumping" of DSM altogether in favor of disease codes of ICD 10.

The overarching problem of current DSM is that it lacks a coherent conceptual model of psychiatric illness, that in the light of modern understanding, it is behind the times. In view of the advantages of DSM discussed above, however, what is called for is a reconceptualization, not abandonment, of the multiaxial model of diagnosis.

14.2 What Is Diagnosis?

Diagnosis derives from the Greek *dia*, meaning through or across, and *gnosis*, meaning knowing. Knowing Through, Knowing Across *What?* Hippocrates, the father of medicine, believed "with regard to diseases, the circumstances from which we make the diagnosis are – by attending to the general nature of all, and the peculiar nature of each individual – to the disease, the patient, and the applications – to the person who applies them. . . the patient's habits, regimen, and pursuits. . .thoughts, sleep, or absence of sleep, and sometimes his dreams. . ." (Hippocrates: Of the Epidemics, Section III)(Hippocrates). Diagnosis must be the knowing of the *whole* of the patient. DSM III and IV were attempts toward this goal, though the goal was not explicitly stated, and thus suffered conceptual confusion.

The diagnosis of the whole of the patient must explicitly define the suffering dimension of the patient, *the illness*, and the contributing morphological, physiological, biochemical, genetic *disease or conditions*, the *memes and stresses* that interacted with them, and the *assets* of the patient that protect or mitigate against the noxious forces.

Illness is by definition memetic, i.e., how a person experiences suffering and expresses suffering is determined by prevailing belief systems and imitation of those who suffer from ailments. Illness is often the manifestation of a strife and/or revolution within the patient's memetic brain, caused by stress or other weakening of the dominant selfplexes, resulting in the upsurge of hitherto repressed aspects of the personality.

Medical diagnosis in the last century underwent a major transformation, i.e., from syndromic (illness) to etiologic (disease), largely due to advances in genetics and biochemistry. This spectacularly successful reductionistic approach, however, often led to a lamentable neglect of the patient as a person. Should psychiatry follow the footsteps of medicine? The multiaxial diagnosis in psychiatry potentially allows us to avoid the pitfalls of replacing illness with disease. For psychiatry, at least, both illness and disease have to be recognized and treated. Currently, however, all Axes I and II diagnoses are syndromes, and, as we have noted, each syndrome probably has a number of different genetic/neuroscience underpinnings (disease), each of which, in turn, gives rise to *different combinations of syndromes* depending on developmental history. For example, the 5-HTTLPR *s/s* may underlie depressive syndrome, anxiety syndrome, risk-aversive personality, and irritable bowel syndrome (see Chapter 1 for further discussion of 5-HTTLPR). Should 5-HTTLPR *s/s* replace all of the syndromes as an etiologic diagnosis, at the expense of knowing what the patient's suffering is?

We need a separate axis for the psychiatric illness, the *memetic,* phenomenological, experiential dimension of the patient, such as depression, anxiety, and psychosis *and* a separate axis for the genetic/neuroscience disease diagnosis. The differential diagnosis of the syndrome, e.g., depression, would not be major depression vs. bipolar disorder vs. schizoaffective disorder vs. mood disorder secondary to general medical condition vs. substance-induced mood disorder. The differential diagnosis would instead be: what are the factors that resulted in a memetic revolution or

memetic war within the brain? What is the extent of contributions to the depressive syndrome by the specific brain dysfunction, to what extent did specific genes and early experiences contribute to the brain's vulnerability to dysfunction, what is the extent substances may also have contributed, to what extent did recent stresses also contribute, are there psychosocial support systems that may be mitigating the extent of depressive memes and thus the depressive syndrome?

When the existence of a genetic/neuroscience disturbance is apparent, then a differential diagnosis of this condition should occur following the medical model. This approach will firmly establish the notion that both the illness (memes) and the disease require attention and care. This approach would also apply to general medicine.

14.3 Psychiatric Diagnosis: Dysregulation and Final Common Pathway Syndromes, Resurrection of Neurosis

As discussed above, medical diagnosis saw a shift from syndromic diagnoses (e.g., consumption, grippe) to etiologic and laboratory diagnosis (e.g., tuberculosis, Type I diabetes mellitus, hyperlipidemia). With the advent of DSM III and IV, it was hoped that the psychiatric disorders, as with medical illnesses, would give way to discrete etiologic diagnoses underlying them, perhaps, schizophrenia Type I that would turn out to be associated with a discrete gene mutation. Research has shown, however, that there are numerous "vulnerability" genes that subserve normal functions but may also, in some instances, cause certain aspects of a syndrome (e.g., psychosis in mood disorders, depression in anxious patients).

Our new model is a continuum model with genetic endowment for adaptive function that may become dysfunctional. Of course, there are exceptions, such as a detrimental mutation. There is also the possibility of *cliff edge phenomenon*, where an increased expression of an evolutionarily adaptive genetic trait may reach a point of sudden maladaptiveness, perhaps as in the case of vigilance (Nesse, 2004).

Most psychiatric conditions are syndromes of dysregulation. The dysregulation may be a reflection of memetic conflict or memetic turmoil, or it may reflect an epigenetically unstable limbic structure, which in turn is activated by incoming memes. Anxiety is normal and necessary, but when it becomes panic, and repeated without provocation, it is dysregulated anxiety and needs treatment. So is sadness and depression, vigilance and paranoia, creativity, "out of the box thinking" and psychosis. So is brave exploration and antisociality. The sharp distinction between normality and psychiatric disorder, and one psychiatric disorder from another, of DSM III and IV has served its purpose in obtaining reliable syndromic populations to study. The syndromes turned out to be continuums and genetically heterogeneous. We must discard the categorical approach. We should also recognize personality traits and symptoms that border between normality and serious autonomous psychiatric syndromes. I suggest resurrecting the term *neurosis*.

Discarding the categorical approach does not mean that we should not have a line of distinction between neurosis and major psychiatric syndromes. Major psychiatric

syndromes, such as the depressive syndrome and psychosis, however, should be a designation of the expectable autonomous course of the illness rather than mutually exclusive categories. Such major psychiatric syndromes are final common pathway syndromes that reflect a common brain functional pathology (e.g., hyperactive D2 receptors in the mesolimbic system) with heterogeneous genetic, biochemical, and memetic contributions (e.g., drug induced psychosis). One patient may have multiple psychiatric syndromes as well as neuroses.

Neurosis serves as an intermediate diagnosis between normality and major final common pathway syndromes and would encompass various traits and symptoms that represent gene × meme interaction (interaction includes simple additive effect as well as synergy and mitigation) and early learned behaviors. Neurosis would include such symptom complexes and personality patterns as generalized anxiety, phobias, minor depression, schizotypal and avoidant personalities and the borderline syndrome.

The evidence that psychotherapy affects the brain function/structure (Goldapple et al., 2004; Kandel, 1979, 1998; Paquette et al., 2003; Roffman et al., 2005) further provides the necessity to reintroduce the notion of neurosis as the psychotherapy thereof may actually prevent the full development of a major syndrome, as would other preventive measures such as social support and protection of children from violence and abuse.

There is overwhelming evidence that social support mitigates against stress and the precipitation, maintenance, and prognosis of symptoms of major psychiatric disorders (Brugha, 1995; Norman et al., 2005; Silver et al., 2006; Surkan et al., 2006).

The multiaxial system begun with DSM III has to be modified to be compatible with the new model, and should be a *diagnosis* in its original sense, i.e., a thorough knowing of the patient.

The new system should clearly delineate the phenomenological/memetic illness dimension of the patient from the potential genomic/brain morphological and functional states and the interacting stresses and protective assets of the patient. The new system, therefore, must have three new entities reflected in the axes: (1) the genomic/brain morphological/functional dimension, which we will call the geno-neuroscience diagnosis, (2) early, recent, and current stress, and (3) the protective psychosocial assets of the patient.

In addition, the new system should have a separate axis for *formulation*, an integration of the entries in all the axes in managing the person who is the patient.

14.4 Proposal for a New DSM Scheme

I propose that the axes of the new DSM consist of the following:

Axis I: Memetic/phenomenological (neurophysiomemetic) diagnosis: psychiatric syndromes, traits, and symptoms, based on deviations of normal brain function.

Axis II: Geno-neuroscience diagnosis: genes, brain morphology, biochemistry and pathology, functional changes and conditions independent of, but potentially influencing Axes I and III.
Axis III: Medical diseases and condition.
Axis IV: Stresses – childhood, recent past, and current.
Axis V: Psychosocial assets: protecting and/or mitigating against disease and functional state, past 5 years and current.
Axis VI: Biopsychosocial and epigenetic formulation.

Each axis is conceptualized to influence each other and provides a snapshot of the major factors that must be considered in the pathogenesis and/or management of Axes I and II.

14.4.1 Axis I: Memetic/Phenomenological (Neurophysiomemetic) Diagnosis: Psychiatric Syndromes, Symptoms, and Traits, Based on Deviations of Normal Brain Function

This axis will represent the phenomenological *psychiatric illness* of the patient. This approach accepts the suffering dimension of the patient on its own level, no matter what the underlying etiology. The emphasis here is what memes are emitted by the patient, and what dysfunctional memes may be out of control within the brain. The diagnostic terms will be familiar psychiatric syndromes, but the memetic nature of diagnosis has to be considered.

I suggest that the syndromes be classified in six broad categories based on deviations of normal brain function in a continuum of severity and manifestation.

A. Attention-cognition spectrum syndromes (delirium, dementia, impulse control syndromes, ADHD, antisocial personality, obsessive-compulsive personality traits, obsessive-compulsive syndrome).
B. Fear–anxiety–depression Spectrum Syndromes (anxiety, panic, phobias, ASD, PTSD, borderline personality, dependent and avoidant personalities, social phobia, bipolarity and mania, depression – neurotic and syndromic, adjustment disorders).
C. Reality perception spectrum syndromes (psychosis, dissociation, conversion, somatoform, misattribution somatization).
D. Pleasure-motivation spectrum syndromes (substance use/abuse, addictions to substances and beliefs, fanaticism).
E. Primary memetic syndromes (eating disorders, factitious disorders, malingering, meme-directed destructive behaviors).

These categories are not mutually exclusive, and each entity within the categories may have subtypes and degrees of severity specified. For example, anxiety-situational, anxiety neurosis, major depression, psychosis – acute, Type I, bipolar syndrome – Type I, cognitive syndrome – delirium superimposed on dementia.

See Part IV for further discussion of each of the categories.

Currently, Axis I diagnosis is of limited value in psychopharmacology as the drugs are the same for most cases of schizophrenia, schizoaffective disorder, bipolar disorder, major depression, etc. The reason for this is that the categories do not overlap but the symptoms (phenomenology) for which treatment is directed do. Thus, it makes better sense to classify Axis I in large clusters of symptoms for which symptomatic treatment may be indicated.

Axis I often indicates a state of pathologic *replication* of memes such as anxiety and depression. The cause of replication of the memes may be an overwhelming influx of new memes (situational), the continuing conflict among resident relatively dormant memes causing ebb and flow of replication, or reawakening of some dormant memes causing new conflict with dominant ones (neurotic), or may be a final common pathway major psychiatric syndrome from a culmination of any of the memetic and genetic factors (syndromic). It may also be a primary memetic syndrome based on imitation, such as malingering, factitious syndromes, or suicide bombing.

The diagnoses in Axis I can and often would be overlapping. Thus, a patient could be diagnosed with obsessive-compulsive personality trait; obsessive-compulsive syndrome; depression, neurotic; and depression, syndromic. The diagnosis would not use rigid diagnostic criteria but list one or more characteristic features that may be memetic (e.g., low self-esteem) or physical signs (e.g., anorexia). This scheme is compatible with current medical diagnostic practice where hypertension, hyperlipidemia, edema, nephrotic syndrome, diabetic nephropathy, and Type II diabetes mellitus might be diagnosed in the same patient.

Who should make Axis I diagnosis? As currently is the practice, any qualified mental health professional should be able to make the phenomenological Axis I diagnosis, unlike Axis II diagnosis below, which should be made only by a qualified medical professional.

14.4.2 Axis II: Geno-Neuroscience Diagnosis: Genes (Including Family History of Psychiatric Illness), Brain Morphology, Biochemistry and Pathology, Functional Changes and Conditions Potentially Influencing Axis I

I expect that this category will be a work in progress for a while as potential diagnoses in this axis have so far been thought of as mere biological underpinnings of Axis I. As discussed above, Axis I syndromes should be conceptualized as symptomatic manifestations of heterogeneous entities, some with major geno-neurobiological and epigenetic contribution, and others with much more contribution by situational and memetic factors. Thus, Axis II should not be conceptualized merely as biological underpinnings of Axis I, but rather independent genetic/neurobiologic diagnoses that may or may not contribute to the behavioral/emotional phenotype in Axis I. In fact, it may explain Axes III and V

rather than Axis I as in a patient with irritable bowel syndrome and 5-HTTLPR *s/s* genotype whose anxiety is only moderate. In fact, some Axis II diagnoses are more likely to be the biological underpinnings of psychological and physical *dispositions* equally relevant to medicine and psychiatry. By establishing Axis II as an independent dimension for geno-neurobiological state, we can eschew the unnecessary argument as to whether the psychiatric syndrome in Axis I is "biological" or "psychological" in origin. It also obviates the futile quest for finding the biological underpinnings of arbitrarily defined Axis I disorders (Frances and Egger, 1999).

For Axis II, we may be initially content with neurobiologic findings on imaging and known genetic factors, e.g., low hippocampal volume and enlarged amygdala, hyperactive subgenual anterior cingulate, 5-HTTLPR *s/s*.

The entities in Axis II would eventually illuminate, together with Axis IV, how Axes I, III, and V may have evolved as well as suggesting potential intervention specifically designed for the neurocircuit dysfunction which may be both pharmacologic and psychotherapeutic. Until such refinements occur, any identifiable putative biological factors should be listed here, including gene variations as in 5-HTTLPR, MAOA, and DAT1. It should also include abnormalities in brain imaging studies including MRI, fMRI, SPECT, PET, and CT. Significant family history of psychiatric illness should be also noted here.

These conceptualizations of Axes I and II will promote research as tests for associations and correlations among items between the axes are likely to reveal new ways in which psychiatric syndromes, personality traits, etc., are associated with specific genes and specific areas and functions of the brain.

14.4.3 Axis III: Medical Diseases and Conditions

This axis would list medical conditions and diseases that may coexist with the mental condition.

14.4.4 Axis IV: Stresses: Childhood, Recent, and Current

Entries in this axis are the factors that potentially contributed to the personality trait and neuroses and may have set the stage for the major psychiatric syndrome in Axis I. In contrast to DSM IV, I propose that we specifically list major stresses in childhood, as well as recent and current stressors.

14.4.5 Axis V: Psychosocial Assets and Recent/Current Functioning

A thorough knowing of the patient is not possible without considering the assets as well as liabilities of the patient. This axis should provide information about the protective and mitigating factors for health rather than illness. They would include

intelligence, educational level, school and work history, and social support. I would propose maintaining the global assessment of functioning of the current DSM at the end of Axis V, but extend the GAF for past year to past 5 years to account for functioning before recent stresses in Axis IV, to express it in a single fractional number: Previous 5 years GAF/ Current GAF. Expressed as: 70/40.

14.4.6 Axis VI: Biopsychosocial and Epigenetic Formulation

This axis is an integration of the previous five axes as they apply to the person who is the patient. Genetic factors such as family history should be considered in the light of early memetic experiences including abuse and nurturing. The illness on Axis I, neurobiologic findings on Axis II and physical conditions in Axis III should be integrated with recent and current stressors, social support, and functioning levels in Axes IV and V. This integrated formulation should lead to a rational memetic and genetic management plan for the patient.

14.5 An Illustrative Case

A 48-year-old married Hispanic female, currently unemployed, was admitted to the medical service for exacerbation of gastroenteritis. A psychiatric consultation was requested because she was observed crying, and stating that life was not worthwhile living.

Medical history revealed that the patient developed gastroenteritis from an early age, with frequent bouts of diarrhea and abdominal pain. She had multiple medical admissions for this. She was also diagnosed with hepatitis C associated with intravenous drug use. Upon admission, she had hyponatremia and hypokalemia, which have been corrected. Her liver function test was within upper normal limits.

Psychiatric consultation interview revealed that the patient has long-standing depression with bouts of exacerbation, as well as nightmares and flashbacks of childhood abuse of several years' duration, including physical and sexual abuse. She was second of six siblings, had never known her biological father, had been abused by her stepfather. Her mother and stepfather were both migrant field workers. She had dropped out of school in the eleventh grade to be married to an abusive husband, which resulted in a divorce within 2 years. She used many substances since the age of 14, including alcohol, marijuana, heroin, and methamphetamine. After her divorce, she worked in various menial jobs and obtained her GED by attending an adult school. She then attended a school to become a cosmetician and worked in that capacity for several years, and married her current husband, who is a mechanic and a caring, non-abusive person, and had two daughters. She had by then stopped using substances heavily.

Her family history revealed very little concerning her biological father, whom she never knew, other than that he used substances. Her mother was described as

being an ineffectual person who was unable to protect the patient from the abusive stepfather. Her mother also had bouts of depression, and was considered to be a very rigid, religious, and superstitious person. The family was Catholic. The patient herself had been religious and attended church regularly until about 2 years ago, but currently she does not as she "lost faith."

The patient had very little contact with her mother or stepfather since she left home, but she knows that they both died about 5 years ago. Her older daughter, age 18, was killed in an automobile accident 2 years ago, after which her gastroenteritis flared up, and she had to stop working. She started using methamphetamine heavily again. Upon questioning, the patient admitted that she is currently undergoing menopause, and has hot flashes and mood changes. She is not on hormone replacement therapy.

The patient's husband describes the patient as a loving but anxious person, who tends to become preoccupied with worries, and tends to become compulsive when stressed. For example, she would clean the house several times a day, call her husband and daughter several times a day to make sure they are OK. He also noted that the patient's gastrointestinal problems get worse when she is anxious, particularly since the tragic death of their daughter. He also stated that the patient frequently wakes up from sleep with nightmares and that she has been using methamphetamine especially since their daughter's death.

Mental status examination revealed a rather thin Hispanic woman appearing her stated age, wearing hospital attire. She showed rather labile affect, particularly when talking about her deceased daughter, her mood was depressed, and had passive thoughts of wishing she would die, had hopeless and helpless feelings. She admitted to an exacerbation of insomnia and nightmares, of seeing her deceased daughter as well as the patient's childhood abuse. Although the chart noted that the patient was disoriented upon admission, at the time of the interview, the patient was cognitively intact, and showed good abstraction and judgment.

Genetic testing revealed 5-HTTLPR *s/s* genotype, and CYP 450 2D6 poor metabolism.

Diagnosis

Axis I:

a. Posttraumatic stress disorder
   –first associated with childhood physical and sexual abuse,
   –exacerbated by abuse by first husband,
   –recently re-exacerbated by her daughter's death.
b. Depressive neurosis associated with 5-HTTLPR *s/s* and PTSD.
c. Depressive syndrome as exacerbation of above, precipitated by daughter's death, contributed by increased substance use and exacerbation of gastroenteritis, menopause.
d. Obsessive-compulsive traits, probably to ward off depression, mimetically associated with mother's obsessive-compulsive traits.
e. Polysubstance abuse, probably to self-treat depression, PTSD symptoms, and physical discomfort.

f. Probable delirium on admission, associated with electrolyte aberrations on admission, now resolved except for possibly labile affect, which may also be associated with menopause.

Axis II:

a. 5-HTTLPR *s/s*.
b. CYP 450 2D6 poor metabolizer.
c. Probable amygdalar hypersensitivity.

Axis III:

a. Chronic gastroenteritis associated with stress.
b. Electrolyte imbalance upon admission associated with above.
c. Hepatitis C associated with intravenous drug use.

Axis IV: Stresses

a. Stresses in childhood
   Childhood physical and sexual abuse
b. Stresses in early adulthood
   Physical abuse by first husband
c. Recent and Current Stresses
   Daughter's death 2 years ago
   Exacerbation of gastroenteritis
   Menopause

Axis V: Psychosocial Assets and Recent/Current Functioning

Assets:
Supportive husband
History of recovery from stress by attending adult school, getting GED, good employment history until death of daughter.

Function (last 5 years/current)
75/55

Axis VI: Formulation

The patient probably has by family history genetic predisposition for depression and obsessive-compulsive traits on her mother's side as well as at least substance abuse on her biological father's side. Further contributing to her depressive neurosis and tendency for depressive syndrome, as well as gastroenteritis, is her genetic status of 5-HTTLPR *s/s*. Further, her hepatitis C associated with early intravenous drug abuse and her status as a poor metabolizer of CYP 450 2D6 enzyme are considerations in using drugs that are metabolized by the liver.

For a patient with her genetic vulnerability to heightened stress response, her early memetic environment of migrant farmers was filled with memes for drug and alcohol abuse and domestic violence. Her stepfather was clearly infected with these memes and physically abused the patient as a child. This early childhood abuse caused an epigenetic cascade resulting in stress-responsive gastroenteritis as well as depressive and obsessive-compulsive neurosis, which led to polysubstance abuse as self-treatment for the symptoms, again an endemic meme, which unfortunately led to increased symptoms in the long run. The patient's inability to assert herself effectively may have been due to infection by her mother's religious memes, some of which may have infected the patient's tendency toward obsessive-compulsiveness. Nevertheless, the patient made surprisingly good adaptation by first divorcing her abusive first husband, then finishing her education, getting out of an abusive first marriage, and working productively as a cosmetologist, for which her obsessive-compulsive traits may have been put to good use. She also married a caring man and had two children. One wonders whether there may have been an unidentified beneficial memetic model for the patient during this period. Reconnecting with this memetic model may be an important factor in planning therapy.

The tragic loss of her older daughter due to a motor vehicle accident, however, resulted in a massive infusion of stress memes, overwhelming her meme-filtering function, and awakening dormant stress memes, resulting in an unchecked replication of hopeless and helpless memes, traumatic memes of physical and sexual abuse, finally culminating in a depressive syndrome as well as a severe exacerbation of gastroenteritis. Memes associated with menopause, such as the loss of reproductive function, may have contributed to the strengthening of her low self-esteem, and the physiologic concomitants of menopause such as hot flashes may have contributed to her lability of affect. Her delirium upon admission was of course a result of the electrolyte imbalance.

Therefore, the treatment planning should proceed at a multiple levels:

Treatment:

1. Depressive Syndrome, Depressive Neurosis:

    a. Gene-Oriented Rx:
    Depressive syndrome is a final common pathway syndrome requiring both gene- and meme-oriented treatments. In view of her hepatitis C and her CYP 2D6 poor metabolizer status, drugs that are metabolized by the liver, and especially by this enzyme must be used with caution. As she has severe insomnia, and her anorexia associated with her gastroenteritis and depression, an antidepressant that induces sleep and increases appetite, and has an alternative metabolic pathway to CYP 450 2D6 would be ideal. In view of her 5-HTTLPR *s/s* status, an SSRI may not be effective. Mirtazapine is a non-SSRI drug that has both serotonergic and noradrenergic action, induces sleep, and enhances appetite. It is metabolized by both CYP 450 2D6 as well as CYP 450 3A4, an alternative pathway to 2D6. While mirtazapine

is metabolized by the liver, her normal liver enzyme levels indicate that use of this drug is not contraindicated. Thus, mirtazapine 15 mg hs was recommended.

b. Meme-Oriented Rx:
The patient had overwhelming proliferation of depressive memes that had to be controlled. Hospitalization was recommended as a broad-spectrum meme-oriented therapy, to change the source of incoming memes in a controlled setting, and to provide augmentation of meme-filtering activity. Hospitalization also provides such diversionary activities as occupational and recreational therapy.
After the hospitalization, the patient should receive outpatient meme-oriented therapy which would include stress management techniques which would be conducive to both depressive syndrome and depressive neurosis, as well as the stress-responsive gastroenteritis. She should also receive specific memes as education concerning menopause. Cognitive-behavioral therapy geared to building self-esteem memes would be effective as well as interpersonal therapy directed to resolving the grief over her daughter's death.

2. PTSD
Gene-oriented therapies include use of antidepressants as described above. Specifically for the nightmares, Prazocin 1–6 mg per night may be tried. The patient received optimal relief with Prazocin 3 mg hs.

Meme-oriented therapies for PTSD would include all broad-spectrum meme-oriented therapies including stress management, relaxation training, music, and dance therapy, etc., as well as specific meme-oriented therapies such as recounting traumatic events with suppression of physiologic arousal with propranolol, cognitive-behavioral therapy, etc.

3. Obsessive-Compulsive Traits and Substance Abuse
In this patient, both obsessive-compulsive traits and substance abuse seem to be attempts to manage and self-treat depression and PTSD. Thus, the treatment of the latter conditions may resolve these conditions. Exploration and understanding of the memetic component of her obsessive compulsive traits as an imitation of her mother's coping strategy may be helpful, as well as her infection by her father's substance abuse memes that resulted in her hepatitis C. Providing alternative means of deriving pleasure, such as through relaxation training, music, dance, massage therapy, may be also helpful.

An avatar, constructed by the patient in collaboration with the therapist, who is endowed with the attributes that the patient wishes to achieve, may demonstrate to the patient that she can, indeed, emulate herself behaving and feeling self-confident, assertive, and in control in virtual reality, which will eventually transform itself into reality itself.

I wondered in the formulation above whether the patient had an unidentified memetic model during the period when she divorced her first husband and went back to school to become a cosmetologist. In fact, it turned out that the patient had

made friends with an older woman, Rema, who was herself a cosmetologist. The patient had gradually lost contact with Rema who had moved to another city. When the patient was reminded of that relationship, she successfully reconnected with her and has weekly phone conversations with her. The patient considers talking with Rema regularly to be a great part of her current psychotherapy.

Note: This chapter is largely based on a paper entitled, *A proposal for a new multiaxial model of psychiatric diagnosis. A continuum-based patient model derived from evolutionary developmental gene–environment interaction*, published in Psychopathology (Leigh, 2009). This chapter, however, explicitly adds the memetic dimension to the paper.

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