Overview of Psychiatric Disorders and the Role of Newer Antidepressants

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The Course of Major Depressive Disorder

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Our knowledge of the diagnosis, natural history, and course of major depressive disorder (MDD) continues to evolve as we learn more about the underlying biological processes involved. Susceptibility to major depression based on patterns of gene inheritance or interaction with an individual's environment is an ongoing area of study that will more fully define the course of the illness. Our knowledge of course-specific treatment modalities remains in its infancy, although ultimately it is hoped that it will give rise to regimens designed for specific disease courses.

MDD has a high rate of occurrence, estimated at 17% lifetime prevalence.[1,2] It is probable that 50% of people who experience a single depressive episode will have another.[1] The lifetime course of recurrent unipolar major depression varies. Some people have only a single lifetime episode, but the majority have episodes that occur in clusters or are separated by many years of normal functioning. Between 20% and 33% of individuals with MDD continue to have persistent or residual symptoms that last longer than 2 years.[1] Individuals who continue to meet full *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), criteria for a major depressive episode (MDE) for 2 or more years and individuals who have recurrent MDD without full interepisode recovery with a total duration of illness of 2 or more years are considered to have chronic major depressive disorder.[3]

CHRONIC MAJOR DEPRESSION

Four types of chronic major depressive disorder are recognized in DSM-IV: dysthymia, double depression, chronic major depressive disorder, and major depressive disorder with incomplete interepisode remission.[3] An early onset and a lifetime course often characterize the chronic major depressions. More than 50% of chronically depressed adults have a comorbid personality disorder, and approximately one third have either a lifetime comorbid anxiety disorder or a history of alcohol or drug abuse or dependence.[4,5]

Because of the early onset and continual nature of chronic depression, it accounts for an inordinate proportion of the enormous burden of depressive illness.

Akiskal[6] first noted the general belief among clinicians that chronic depression does not respond favorably to either pharmacotherapy or psychotherapy. Indeed, the expectation in treating chronic depression is for a poorer prognosis, slower response time, and more limited response as compared with nonchronic major depression.

Approximately one third of patients with MDD, or 3% of the U.S. population, suffer from chronic depression.[2,7] Chronic depression accounts for 30% to 35% of all depression.[8] Despite the lower prevalence rate, chronically depressed patients are among the highest users of general medical services.[9] The demographics of chronic depression can be summarized from 2 recent investigations in this population.[4,10] The typical patient tends to be an unmarried, college-educated woman in her early 40s who has a 16- to 18-year lifetime duration of depression. Psychosocial dysfunctionality is reflected in unemployment rates of 15% to 20% in chronically depressed patients.[4]
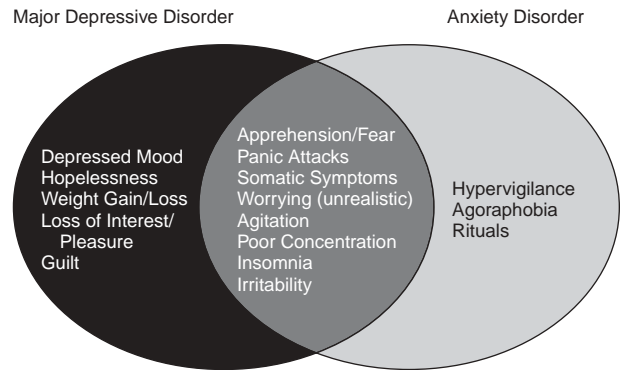
NATURAL COURSE OF DEPRESSIVE ILLNESS

With the recognition that depression is generally chronic and recurrent, one can break down the treatment into 3 phases. The acute phase involves treatment induction and typically lasts 6 to 12 weeks. The continuation phase is generally considered to be 4 to 9 months in duration, and the maintenance phase extends 1 year or more.[11] The goal of treatment is full remission with a return to the premorbid level of function, including restoration of sleep, appetite, and sexual functioning. Terms used to characterize the impact of treatment (generally an antidepressant drug) on the natural course of MDD are *response, remission, relapse, recovery,* and *recurrence*.[11]

Kocsis and colleagues[12] conducted the first controlled, monopharmacotherapy study of long-term maintenance treatment for patients with pure dysthymia, double depression, or chronic major depression. Open-label desipramine was evaluated in a 10-week acute phase, followed by a 16-week continuation phase and a 2-year maintenance phase in which responders were randomly assigned to desipramine or placebo. Of the 50 patients who entered the maintenance phase, 11% randomly assigned to desipramine and 52% randomly assigned to placebo relapsed at 2 years. Most relapses occurred within the first 6 months. In another double-blind, randomized, multicenter trial, the comparative efficacy of sertraline and imipramine as acute, crossover, continuation, and maintenance-phase therapies was evaluated in patients with chronic MDE and double depression (DSM-III-R criteria).[13] The 635 enrolled patients were randomly assigned 2:1 to sertraline or imipramine, respectively. The acute-phase (12-week) results showed a 58% response rate to sertraline and a 61% response rate to imipramine. Thus, a fair number of patients with chronic depression will respond to antidepressant therapy in the acute phase of treatment and, more impor-

tantly, may have lower rates of relapse if the antidepressant regimen is continued as maintenance therapy.

Advancing our understanding of chronic depression even further is the recent *New England Journal of Medicine* publication in which nefazodone, an antidepressant presumably with a trimodal mechanism of action, was compared with a new psychotherapy developed specifically to treat chronic forms of depression (i.e., the Cognitive Behavioral-Analysis System of Psychotherapy [CBASP]) and with the combination of nefazodone plus CBASP for acute, continuation, and maintenance treatment of patients with DSM-IV–defined chronic major depressive disorder or double depression.[4] Results of this landmark study are discussed elsewhere in this supplement (see Schatzberg et al.[14]).

Major Depressive Disorder With Anxiety Symptoms or Sleep Disturbance

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MAJOR DEPRESSIVE DISORDER WITH ANXIETY SYMPTOMS

The relationship between anxiety and depression is complex. In current psychiatric nosology, these constructs are viewed as separate entities with distinct treatments. It is important to distinguish between symptoms of anxiety and depression for diagnostic and treatment purposes, yet one must also recognize the tremendous comorbidity and overlap of symptoms in individuals with anxiety and depressive disorders (Figure 1).[1,3,15,16] While individuals may have coexisting anxiety and depressive disorders, primary MDD is commonly accompanied by substantial symptoms of anxiety, and primary anxiety disorders (e.g., panic disorder, generalized anxiety disorder, social phobia) are commonly accompanied by symptoms of depression.

The term *anxious depression* was initially used to describe individuals with prominent anxiety symptoms in the context of an MDE. While many patients with depressive disorder have additional, discrete anxiety disorders, a residual category of patients with prominent anxiety symptoms who do not meet criteria for a DSM-IV anxiety disorder diagnosis exists. Between 15% and 30% of depressed patients have recurrent panic attacks,[17] and nearly two thirds of depressed patients have other anxiety symp-

Figure 1. Specific Symptoms Common to Major Depressive Disorder and Anxiety Disorders According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[a]

Major Depressive Disorder | Anxiety Disorder

Depressed Mood
Hopelessness
Weight Gain/Loss
Loss of Interest/
    Pleasure
Guilt

Apprehension/Fear
Panic Attacks
Somatic Symptoms
Worrying (unrealistic)
Agitation
Poor Concentration
Insomnia
Irritability

Hypervigilance
Agoraphobia
Rituals

[a]Based on Keller and Hanks,[1] *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,[3] Clayton et al.,[15] and Coplan and Gorman.[16]

toms such as agitation, psychic anxiety, or nonspecific gastrointestinal and other somatic complaints.[15] As many as 85% of adults with depression experience significant symptoms of anxiety,[18] and 58% have a diagnosable anxiety disorder during their lifetime.[19] The risk for MDE is increased by preexisting anxiety disorders, and women are more likely than men to develop an anxiety disorder at an early age.[20] In fact, the presence of anxiety disorder accounts for 50% of the gender-related difference in lifetime MDE.[20]

Mulsant and colleagues[21] reported that one third to one half of elderly psychiatric inpatients and outpatients with major depression have severe anxiety symptoms, but that only 8% have a diagnosable anxiety disorder. Sixty-five percent of elderly nursing home residents with major depression display concurrent symptoms of anxiety.[22] Lenze and colleagues[23] recently showed relatively high rates of current and lifetime anxiety disorders in elderly depressed individuals. In their study, anxiety symptoms were associated with a more severe presentation of depressive illness, including suicidality.

Individuals who suffer from both anxiety and depression experience a more chronic course with greater impairment of social and occupational function than individuals with either anxiety or depression alone. In one study[15] of more than 300 depressed patients, persons with high anxiety took twice as long to recover from the index episode as compared with patients with low anxiety. In another study[24] of depressed patients in a primary care setting, a coexisting anxiety disorder indicated risk for more persistent depression. Patients whose depression is accompanied by an anxiety disorder have fewer personal and social resources, more chronic illness, and poorer treatment response.[25] In individuals with major affective disorder, panic attacks and severe psychic anxiety are associated with suicide.[26]

Pathophysiology of Depression With Anxiety

This strong relationship between anxiety and depression almost certainly has neurobiological underpinnings. Some forms of anxiety and depression may represent different phenotypic manifestations of the same genetic predisposition resulting from varying environmental conditions.[27] Imbalances in serotonergic transmission probably contribute significantly to both anxiety and depressive disorders,[28] which helps to explain the utility of the serotonin reuptake inhibitors (selective serotonin reuptake inhibitors [SSRIs] and venlafaxine) and other serotonergic agents, such as nefazodone, in the treatment of depressive disorders and depression-related anxiety symptoms. Nefazodone, however, differs from SSRIs because of its presumed trimodal mechanism of action. Nefazodone is a potent postsynaptic serotonin-2 (5-HT$_2$) receptor antagonist that also is a moderately potent inhibitor of both serotonin and norepinephrine presynaptic transport proteins. Antagonism and down-regulation of 5-HT$_2$ receptors, in addition to inhibiting serotonin reuptake, are presumed to be responsible for the efficacy of nefazodone in the treatment of depression-related anxiety and agitation symptoms.

Management of Patients With Depression and Anxiety

Successful treatment of a patient presenting with both depression and depression-related anxiety symptoms depends on an accurate diagnosis. Fortunately, many antidepressants effectively alleviate anxiety symptoms. In contrast, many anxiolytics (e.g., benzodiazepines) are ineffective for the treatment of depression. As such, treatment generally begins with initiation of an antidepressant agent. In choosing the appropriate agent for anxious, depressed patients, it is important to select one with a low incidence of drug-induced or activating side effects, such as anxiety, agitation, or insomnia.

Nefazodone may provide some specific advantages for treating the subset of anxious, depressed individuals. In a placebo-controlled comparison, nefazodone and imipramine similarly relieved depressive symptoms, but only nefazodone-treated patients had early and sustained decreases in the Symptom Checklist-90 (SCL-90) anxiety factor score.[29] A meta-analysis of 6 randomized, controlled trials of nefazodone in patients with MDD showed that nefazodone produced earlier and more sustained improvement in agitation symptoms than imipramine or placebo and greater improvement in somatic anxiety.[30] Nefazodone was superior to both imipramine and placebo across several objective measures of depression-associated anxiety symptoms (e.g., Hamilton Rating Scales for Depression and Anxiety, SCL-90) in a retrospective analysis of 2 randomized, controlled trials.[31] Finally, recent data indicate that chronically depressed patients treated acutely with nefazodone experience relief from depression-related anxiety symptoms within 1 to 2 weeks.[32]

MAJOR DEPRESSIVE DISORDER WITH SLEEP DISTURBANCE

Several decades of neuropsychiatric research have confirmed the association between affective disorders and sleep disturbance. An estimated 19.3% of a U.S. population sample has suffered from a mood disorder in their lifetime,[2] and researchers speculate that more than 80% of these patients report symptoms of disturbed sleep.[33] With one third of our lives spent sleeping, sleep disturbance plays a vital role in mood regulation and symptom reemergence. Close monitoring of sleep has become an important part of psychiatric practice.

Normal Sleep Architecture

Sleep comprises 2 physiologic states: non–rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM comprises 80% of a normal night's sleep and includes sleep stages 1 through 4. Most psychological and physiologic functions are markedly reduced during NREM sleep.[34] During NREM sleep, significant alterations in endocrine function occur, including secretions of growth hormone, prolactin, and luteinizing hormone and decreases in thyroid-stimulating hormone and adrenocorticotropic hormone.[35,36] REM is a quantitatively different sleep characterized by a highly active brain and physiologic activity levels similar to wakefulness. REM sleep appears to be necessary for learning, memory, and cognition[37] and is probably regulated by the circadian pacemaker located in the hypothalamic suprachiasmatic nucleus.[38] Alterations in normal sleep architecture may predispose individuals to a host of psychological and physiologic problems.

Sleep Abnormalities in MDD

By electroencephalographic (EEG) criteria, 90% of patients with untreated MDD have sleep disturbances.[34] The most common are increased sleep latency; decreased deep, slow-wave sleep (stages 3 and 4); poor sleep efficiency (characterized by intrusions of wakefulness); and reduced total sleep time (REM plus NREM).[39] The precise effects of depression on REM sleep are unclear, but alterations in REM latency, density, and activity have been noted. The relationship of changes in sleep architecture to the therapeutic effect of antidepressant agents also is unclear.[40]

Sleep regulation differs substantially between men and women. Marked decreases in slow-wave sleep in early adulthood have been noted in men but not women.[41] Depressed women show greater EEG dysregulation than depressed men during sleep.[42] The period of childbearing is associated with nearly universal reports of disturbed sleep late in pregnancy and in the early postpartum weeks.[43] Researchers have also demonstrated a relationship between sleep efficiency, mood, and thermoregulation in women. As compared with placebo, estrogen replacement therapy

Table 1. Summary of Objective Electroencephalographic Sleep Measures With Nefazodone and Fluoxetine in Depressed Patients[a]

Variable	Nefazodone	Fluoxetine	p Value[b]
No. of awakenings	↓	↑	≤ .01
% Awake time[c]	↓	↑	≤ .01
% Stage 1 sleep	↓	↑	≤ .01
Sleep efficiency	↑	↓	≤ .01
Sleep latency	↔	↔	NS

[a]Data from Rush et al.,[56] Armitage et al.,[59] and Gillin et al.[60]
Abbreviation: NS = not significant. Symbols: ↓ = decrease,
↑ = increase, ↔ = no change.
[b]Difference between drugs in change from baseline.
[c]Includes awake and movement time by electroencephalograph.

significantly reduces wakefulness in perimenopausal women complaining of insomnia, mood changes, and hot flashes.[44]

Normal aging is associated with subjective and objective alterations in sleep quality; the most consistent are increased awakenings and decreased deep, slow-wave sleep.[45] Late-age sleep deterioration is influenced by several psychosocial factors, including gender, major life events (e.g., bereavement), and ongoing strains such as those arising from chronic medical illness.[46] Current sleep research in older adults points to a relationship between age-related changes in endocrine-metabolic functions and sleep quality,[47] and strategies that focus on these relationships may lead to beneficial effects on body composition and function.[47,48]

Sleep disturbance or deprivation can be lethal; a decrease in sleep of only 1.5 hours a night can reduce daytime alertness by 33%.[49] Sleepiness may be a contributing factor in up to 30% of traffic accidents,[50] and many major industrial catastrophes can be linked to sleepiness.[34] Results of a recent meta-analysis showed that sleep deprivation seriously impairs human functioning, with evidence that mood is more strongly affected than either cognitive or motor function.[51] Unrelieved global insomnia has been shown to be a predictor of suicide within 1 year in patients being treated for MDD.[26]

Management of Depressed Patients With Sleep Disturbances

Treatment for depressed patients presenting with depression-related sleep disturbances ranges from behavioral strategies[52] to antidepressant medications.[39] The EEG sleep profiles of depressed patients are relatively less responsive to psychotherapy because of a constellation of neurophysiologic disturbances that may interfere with the response to behavioral approaches.[53] Findings from a recent chronic depression study[54] suggest that depressive sleep disturbances are not readily responsive to psychotherapy. Rather, insomnia, in the context of depression, is likely to be more responsive to pharmacotherapy with an antidepressant agent that improves sleep.

In choosing an appropriate antidepressant for patients with depression-related sleep disturbances, it is important to select one that is unlikely to cause nocturnal awakenings. Antidepressants that stimulate 5-HT$_2$ receptors, such as SSRIs and venlafaxine, increase nocturnal awakenings and may compromise patient compliance and prognosis.[55–57] In contrast, nefazodone blocks 5-HT$_2$ receptors, and short-term, double-blind, comparative studies[56,58–60] with fluoxetine indicate that nefazodone indeed offers specific advantages for the treatment of this subset of depressed individuals (Table 1).

Antidepressant Selection: Focus on Nefazodone

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Therapeutic options for the treatment of MDD include psychotherapy, pharmacotherapy, electroconvulsive therapy, alternative or herbal therapy, and various combinations of these. It is generally accepted that most antidepressants demonstrate similar short-term response rates. It is also accepted that patients should be maintained on full-dose medication for 4 to 9 months after remission of depressive symptoms. In long-term studies, both SSRIs and nefazodone provide effective relapse prevention.[61,62]

Because limited data exist to predict whether a patient's depression will respond to a particular antidepressant, the clinician must consider several factors when selecting an antidepressant. In patients with a personal and/or family history of depression, the clinician may consider the past response to a medication. Another factor is the particular type of depression being treated. For example, nefazodone,[63,64] venlafaxine,[65,66] and bupropion[67] are effective in treating severely depressed inpatients. Nefazodone is effective for treating all ranges of severity of MDD.[63,68,69] Desipramine,[12] imipramine,[10] sertraline,[10] and nefazodone[4] have all been shown to be effective in chronically depressed patients.

In the absence of a treatment history or for when patients are switched from an antidepressant because of treatment failure or poor tolerability, the adverse effect profile of an antidepressant becomes important; two thirds of patients discontinue therapy because of side effects.[70] Specifically, sexual dysfunction, weight gain, or insomnia may affect a patient's willingness to comply with the regimen on a long-term basis. Nefazodone causes minimal

sexual dysfunction,[71] and it is considered weight neutral[4] (data on file, Bristol-Myers Squibb Company). Nefazodone also has a beneficial effect on sleep architecture in depressed patients with sleep disturbances.[56]

Finally, other considerations when selecting an antidepressant include the potential for drug-drug interactions, medication cost, concomitant use of anxiolytics or sedative-hypnotics, and safety in overdose, as well as uses for the agent beyond treatment of MDD. These issues, and the specific role of nefazodone, are discussed elsewhere in this supplement.

Drug names: bupropion (Wellbutrin and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), nefazodone (Serzone), sertraline (Zoloft), venlafaxine (Effexor).

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