Understanding Depression: A Long-Term, Recurring Disorder

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *summarizes the highlights of a symposium entitled "Mending Minds With Medicine," held September 22, 1999, at the 12th Congress of the European College of Neuropsychopharmacology (ECNP) in London, U.K.*

This symposium was chaired by Stuart A. Montgomery, M.D., Professor of Medicine, Imperial College of Science, Technology and Medicine, London, U.K. The other participants were Giorgio Racagni, M.D., Scientific Director, Centre of Neuropharmacology, University of Milan, Milan, Italy; David J. Nutt, D.M., Professor of Psychopharmacology, Psychopharmacology Unit, University of Bristol, Bristol, U.K.; Alan F. Schatzberg, M.D., Professor and Chairman, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, Calif.; Siegfried Kasper, M.D., Professor and Chairman, Department of General Psychiatry, University of Vienna, Vienna, Austria; and Michael E. Thase, M.D., Professor of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

This symposium and these ACADEMIC HIGHLIGHTS were sponsored by an unrestricted grant from Pharmacia.

Introduction

Professor Montgomery opened the symposium with some revealing facts illustrating the wide-ranging impact of depression on the individual, the immediate circle of contacts, and society as a whole. Lifetime prevalence of depression in the United States has been estimated at 17%.[1] Interestingly, the prevalence rates vary considerably between different countries. Whether this is a true reflection of cultural variation in the incidence of depression or whether the rate of reporting and detecting depression differs by country is not clear.

According to a recent World Health Organization (WHO) report, depression is by far the leading cause of disability: a survey of disabilities experienced throughout the world in 1990 found that more than 1 in every 10 years lived with a disability was due to unipolar depression.[2]

This burden also affects family and friends and has many implications for society in terms of health care use and lost productivity. The Depression Research in European Society (DEPRES) study reported that people with major depression lost 4 times more working days than nonsufferers.[1] Social impairment—the decreased ability to interact with social and work contacts—is increasingly being recognized as a significant manifestation of depression. There is little information available on the role of antidepressants in alleviating social impairment, and it is not known whether drug treatment acts directly on biological systems that affect social functioning or via clinical improvement of the depression. In addition, little is known about how social functioning fits into the monoamine hypothesis of depression, for example, whether either serotonin or norepinephrine has a dominant effect.

Depression is typically a long-term, recurrent illness. Data from the study of long-term maintenance of recurrent unipolar major depression[3] show that more than 40% of patients who recover from an episode of unipolar depression experience a recurrence after 2 years, rising to 60% after 5 years. Furthermore, in approximately one third of patients experiencing an episode of depression, the depression is chronic, lasting at least 2 years.[3]

In citing data from the DEPRES study, Professor Montgomery stated that of a total of 75,000 adults across Europe, almost 17% were suffering from depression,[1] and 43% of those adults had not consulted a physician. Of those who had, 70% had been given no medication for depression, and only 10% of patients with major depressive disorder had been prescribed an antidepressant. In light of the fact that around 70% of patients respond well to antidepressant therapy,[4] it seems that there is still a lot of mistrust of the treatments available and misunderstanding of the disease.

There are currently a range of antidepressants available, with a variety of different mechanisms of action. The most recently developed is reboxetine, a selective norepinephrine reuptake inhibitor (selective NRI). As well as being welcome additions to the range of antidepressants available to the physician, selective serotonin reuptake inhibitors (SSRIs) and reboxetine have also proved to be invaluable tools in

further elucidating the biological basis of depression.

An improved understanding of the biochemical and physiologic basis of depression is necessary to create an improved awareness of its etiology and a greater acceptance of its treatment by drug therapy.

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The Role of Neurotransmitters in Depression

The current understanding of the biological basis of depression was the subject of the presentation by Professor Racagni. A great deal has been learned in recent years regarding the pathophysiology of the brain, although much remains to be elucidated. The "monoamine hypothesis" was proposed over 30 years ago and is based on the theory that depression is the result of a dysfunction in the noradrenergic and/or serotonergic neurotransmitter systems.[1–3] Numerous experimental and clinical reports substantiated this hypothesis, with increasing awareness of the cellular basis of the dysfunction.

Depletion studies have shown that a dietary depletion of tryptophan, the precursor of serotonin, can result in a return of depression in patients in remission.[4,5] Norepinephrine depletion by inhibition of the enzyme tyrosine hydroxylase has had a similar effect.[6] These studies confirmed the hypothesis that both neurotransmitters are involved in depression. However, depression could not be induced by either of these methods in subjects who had not previously experienced depression. The dysfunction is therefore likely to involve more than just a simple monoamine deficiency at the synaptic junction, and there is evidence to suggest that there may be dysfunction at subcellular levels, involving receptors, secondary messengers, and gene regulation.

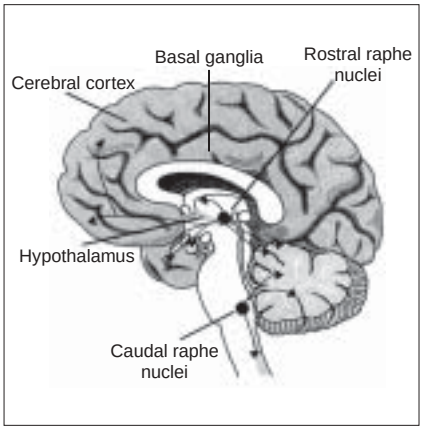
The majority of antidepressants exert their main effect by increasing availability of a neurotransmitter. One of the limitations of the brain physiology–functionality model is that it does not adequately explain why the therapeutic effects of a reuptake inhibitor may not become apparent for several weeks, despite the fact that the drug's defined action is almost immediate. This delay may be due to the time taken for desensitization and down-regulation of the receptors and to neuroplastic changes.[7]

Knowing something of the neurophysiology of depression allowed the development of specifically targeted antidepressant drugs. The SSRIs were the first such antidepressants designed with the particular aim of molecular targeting. Because the SSRIs have been available for some time, whereas reboxetine, a unique selective NRI, has been developed only relatively recently, much more is known regarding the specific role of serotonin in depression than of norepinephrine. Observation of the effects of SSRIs has enabled clinicians and researchers to analyze specifically the function of serotonin in the central nervous system.

The principal centers of serotonergic neurons are the raphe nuclei of the midbrain, pons, and medulla. From these sites axons descend to the cerebral cortex, basal ganglia, limbic cortex/hippocampus, and hypothalamus (Figure 1). In addition, axons from the raphe nuclei in the brain stem descend to the medulla and spinal cord. The initial, immediate effect is blockade of the serotonin transporters at the dendrites and axon of the serotonergic neurons. Serotonin levels initially increase in the somatodendritic area only, causing a down-regulation of somatodendritic serotonin-1A (5-HT_{1A}) autoreceptors. This in turn leads to a loss of regulation of impulse flow in the neuron. Consequently, serotonin is released from the presynaptic axon terminal, and the concentration is increased at the postsynaptic receptor sites.

There are at least 3 distinct classes of serotonin receptor, and possibly up to 14 receptor subtypes. The increase in serotonin availability subsequent to administration of an inhibitor of serotonin uptake is common to all these pathways and all receptors. Since these receptors are present in different functional systems in the body and mediate different responses, the effects of increasing serotonin availability are many and varied. Some of these effects are potentially therapeutic, while others are unwanted side effects. For example, depression is thought to involve the 1A, 2A, and 2C serotonin

Figure 1. Serotonergic Pathways in the Central Nervous System



receptors in the prefrontal cortex, and panic may be mediated by 1A, 2A, 2C, and 3 receptors in the limbic system and hippocampus.[8,9] Conversely, stimulation of the 5-HT_3 receptors in the brain stem vomiting center is thought to cause the gastrointestinal side effects associated with the SSRIs, and stimulation of the 5-HT_{1D} receptors in the vascular system may cause headache and migraine.[10]

The noradrenergic system is less well characterized. This is primarily because the comparable "tools" were not available with which to investigate the noradrenergic system until the availability of the selective NRI reboxetine.[11] The principal origin of noradrenergic neurons in the brain is the locus ceruleus. From this site, axons project to the frontal/prefrontal cortex, cerebellum, thalamus/hypothalamus, limbic system, and spinal cord. The most important pathway with regard to depression is the one innervating the prefrontal/frontal region. However, noradrenergic neurons in the limbic region are also thought to be responsible for the regulation of mood, emotions, energy, and motivation.

As does the serotonergic system, the noradrenergic system has several distinct receptors in different locations. Adrenergic receptors can be classified into a number of different subtypes. In depression, the most important adrenergic receptors are thought to be the α_2 and β_1 subtypes, in particular the β_1 receptors in the cortex. Studies of the receptors have revealed adaptive changes in the receptors in patients with depression. One of the most consistent changes is the increase in the density of β-adrenoceptors on the lymphocytes of patients with depression and in the frontal cortex of suicide victims.[12] This observation has resulted in the down-regulation of β-adrenoceptors being regarded as a marker of antidepressant efficacy.[12,13] The density and affinity of presynaptic α_{2A}-adrenoceptors have also been found to be increased in the brains of patients with depression who committed suicide.[14,15]

Table 1. Effects of Chronic Administration of Reboxetine, SSRIs, and TCAs in Rat Brain[a]

Location/Type of Effect	Reboxetine	TCAs	SSRIs
Norepinephrine-dependent adenylate cyclase	↓	↓	–↓
β-Adrenergic receptors	↓	↓	–↓
cAMP binding to RII	↓	↑	↑
MAP-2 phosphorylation	–	↑	↑
CaM-kinase II activity	↑	ND	↑

[a]Symbols: ↑ = increase, ↓ = decrease, – = no change, –↓ = no change or decrease, ND = not determined. Adapted, with permission, from Brunello and Racagni.[13] Abbreviations: CaM-kinase II = calmodulin-dependent protein kinase II, cAMP = cyclic adenosine monophosphate, MAP-2 = microtubule-associated protein-2, RII = receptor II, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

The time course of response to antidepressants also reveals important information with regard to the effects of increasing neurotransmitter concentrations in the brain. While the inhibition of the reuptake transporters is almost instantaneous, it can be several weeks before an antidepressant effect is seen clinically. This suggests that the chronic "downstream" regulation of the receptors is key to the antidepressant effect.

Professor Racagni emphasized the fact that while the 2 neurotransmitter systems are distinct, they are also interdependent. Patients with depression therefore cannot easily be categorized into 2 classes depending on whether they have a noradrenergic or serotonergic "lesion." However, the interaction between the 2 neurotransmitter systems is not fully understood, and it may be at several functional levels. For example, α_2-adrenoceptors on serotonin terminals are believed to modulate serotonin release at presynaptic terminals.[16] Increased noradrenergic neurotransmission causes stimulation of α_1-adrenoceptors on serotonergic neuron cell bodies, thereby potentiating serotonin release.[17,18] Conversely, there is some evidence to suggest that norepinephrine release may be regulated by serotonin; for example, inhibition of serotonin synthesis has been shown to prevent down-regulation of the β-adrenoceptor by antidepressants.[19,20] It has also been shown in patients with depression that treatment with fluoxetine can affect noradrenergic function,[21] while medication that selectively targets norepinephrine reuptake also increases some aspects of serotonin function.[22,23]

More recently, attention has been focused at the subcellular level, and the noradrenergic system may play a key role in controlling intracellular mechanisms. The stimulation of the α_2-, β_1-, and β_2-adrenoceptors may result in cyclic adenosine monophosphate–mediated intracellular protein phosphorylation, which in turn may activate transcription factors, thereby modulating gene expression. The level of norepinephrine or the status of the adrenergic receptors may therefore influence the expression of serotonin receptors and hence the functioning of the serotonergic system. In vitro work has shown that adrenergic and serotonergic receptors may share common second-messenger pathways through convergence at the level of G proteins (GTP-binding proteins) or effector molecules.[24,25] G proteins may also mediate the regulation of expression of one neurotransmitter receptor caused by stimulation of a different type of receptor.[24] Changes in the expression of subcellular components of the signaling pathways in response to chronic antidepressant administration have already been demonstrated and show distinct between-treatment differences (Table 1). New research in these areas may bring

to light some of the "lesions" that are responsible for depression and may help explain why some patients are responsive to more than one type of antidepressant while others respond more specifically.

Professor Racagni concluded that knowledge of the roles played by both norepinephrine and serotonin is essential for a clearer understanding of how to treat patients optimally. Use of the selective NRI reboxetine will help redress the lack of knowledge concerning the noradrenergic system.

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The Medicine: Current Treatment Advances in Depression

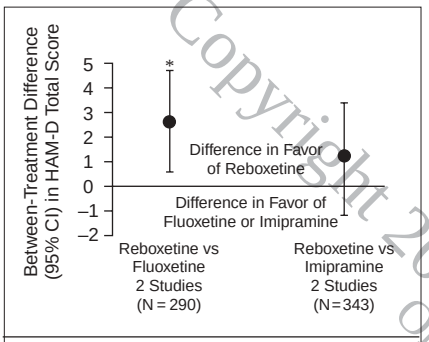
There are 4 main aims of successful treatment of depression, explained Dr. Nutt: to relieve the symptoms of depression, restore normal social functioning, reduce the risk of return to depression, and minimize the adverse effects associated with antidepressant therapy. Antidepressant efficacy must be judged in each of these categories in order to provide the best treatment for the individual with depression.

There are currently over 20 antidepressants available worldwide. The early antidepressants include the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs).[1] The TCAs, which all have a similar chemical structure, interact nonspecifically at a number of receptor sites. The newer antidepressants are uptake inhibitors, including SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and receptor blockers such as mianserin and trazodone.[1]

The most recent class of antidepressants is the selective NRIs.[2] Since the serendipitous discovery of the antidepressant effects of imipramine in the 1950s, TCAs have been the mainstay of the treatment of depression and remain the benchmark against which more recently developed antidepressants have been judged. The TCAs, while effective, are also associated with a range of unwanted side effects such as dry mouth and constipation that limit their use in important patient groups, including the elderly and those with preexisting cardiac conditions. In addition, patient compliance is often compromised due to the poor adverse event profile. An overdose of TCAs can prove fatal.[3]

The development of SSRIs was a major breakthrough. They provide a safer option in comparison with the

Figure 2. Between-Treatment Difference in Mean Hamilton Rating Scale for Depression (HAM-D) Total Score at Last Assessment in Patients Initially Judged as Markedly to Severely Ill on the Basis of the Clinical Global Impressions-Severity of Illness Scale[a]



[a]Reprinted from Montgomery.[12]
Abbreviation: CI = confidence interval.
*p < .05.

TCAs, but also have their shortcomings.[1,3] Although their efficacy has been well documented,[4] they have a distinct adverse event profile, including gastrointestinal events, sexual dysfunction, headache, and anxiety, which may lead to noncompliance.[5] Other drawbacks include the possibility of reduced efficacy over long-term treatment[6] and "discontinuation syndrome."[7]

The most significant advance in treating depression since the advent of the SSRIs has been the development of reboxetine, the first selective NRI, said Dr. Nutt. Reboxetine is a novel antidepressant in that it selectively and potently inhibits norepinephrine reuptake. This is in contrast to the so-called noradrenergic TCAs, such as desipramine, which predominantly inhibit the noradrenergic reuptake transporter but also have a considerable affinity for other receptors. Reboxetine has been shown to have negligible affinity in vitro for serotonin and dopamine uptake sites and for adrenergic and histaminergic receptors, and only weak affinity for muscarinic receptors.[2,8]

Dr. Nutt went on to focus on the clinical studies conducted with reboxetine. A total of 8 randomized, placebo and/or comparator (imipramine, desipramine, and fluoxetine) studies have been conducted in over 2600 patients with major depressive disorder. Reboxetine has been shown to be an effective, well-tolerated treatment for the treatment of depression.[9,10]

Three short-term (4–8 weeks) studies have shown the superior efficacy of reboxetine compared with placebo in adult patients with major depressive disorder.[9] Response rates with reboxetine treatment were as high as 74% and significantly higher than with placebo in each of the 3 studies.[9] When results from all placebo-controlled studies were combined, explained Dr. Nutt, it could be seen that patients treated with reboxetine were significantly more likely (compared with patients treated with placebo) to have a response to treatment that resulted in an improvement of their Hamilton Rating Scale for Depression (HAM-D) score of at least 50%.

The efficacy of reboxetine has been demonstrated to be comparable to that of other antidepressants in a series of studies. Trials in which reboxetine (8–10 mg/day) was compared with imipramine (150–200 mg/day) and desipramine (200 mg/day) showed that more patients responded to reboxetine treatment than to the TCAs and that the mean improvement was greater with reboxetine. Comparison with the SSRI fluoxetine (20–40 mg/day) showed comparable efficacy with reboxetine, both in the number of patients responding and in mean improvement.[9]

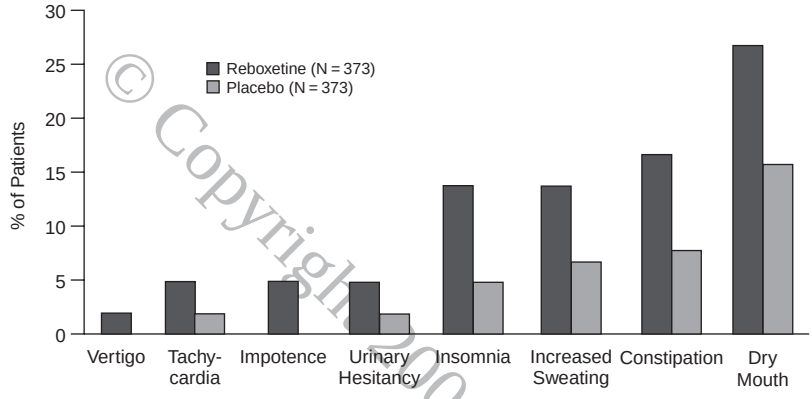
A yearlong, placebo-controlled trial in patients with major depressive disorder found that the efficacy of reboxetine is maintained in long-term treatment, with 78% of patients being classified as in remission by the last assessment.[9] It was calculated that there was a significantly lower chance that patients taking reboxetine would relapse compared with patients taking placebo.[11]

Dr. Nutt also noted that the efficacy of reboxetine has been assessed in patients with severe depression. This was of particular interest since there is already some evidence to show that noradrenergic antidepressants such as venlafaxine, mirtazapine, and milnacipran are more effective than SSRIs in treating severe depression. Reboxetine was found to be significantly more effective than fluoxetine and as effective as imipramine in patients with severe depression (Figure 2), supporting a hypothesis that correcting norepinephrine levels may be necessary for the relief of severe depression.[9]

Efficacy must be combined with good tolerability since early discontinuation of antidepressant therapy leads to relapse in many cases. Depression is a chronic and recurrent illness, and optimal therapy includes continuation and prophylactic treatment, which is jeopardized if the side effects of treatment are hard to tolerate. Early discontinuation increases the risk of suicide and has an economic impact in that it is likely to lead to more hospitalization and more frequent outpatient appointments.[13]

A question frequently raised by physicians is why reboxetine was developed, given that there are many "noradrenergic" antidepressants available, such as desipramine. The benefits are perhaps most obvious when we consider the issue of side effects. Selective reuptake inhibitors have an advantage over TCAs in that their mechanism of action is more precise, being aimed solely at either serotonin or norepinephrine transporters. Our knowledge of neurotransmitter pathways in the brain has helped us to predict and explain the consequences of altering serotonin and norepinephrine availability by using such antidepressants. The gastrointestinal disturbances, increased anxiety, and sexual dysfunction associated with SSRIs are side effects caused by the increased

Figure 3. Frequency of Adverse Events With a Significantly Higher Risk of Development With Reboxetine Than With Placebo (Kaplan-Meier analysis)[a]



[a]Adapted, with permission, from Mucci.[10]

Table 2. Adverse Events With a Frequency of Development Greater Than 10% Occurring in Patients Treated With Desipramine (N = 89), Reboxetine (N = 84), or Placebo (N = 85)[a]

	Frequency of Adverse Event, %		
Adverse Event	Desipramine	Reboxetine	Placebo
Dry mouth*	45	26	21
Increased sweating	28	18	22
Tachycardia	19	12	8
Blurred vision*	17	4	4
Hypotension	13	6	8
Urinary hesitancy	4	12	1

[a]Data from Mucci.[10] Adverse events reported in descending order for desipramine.
*$p < .01$ vs. reboxetine.

levels of serotonin in pathways other than those involved in depression. Selective NRIs, explained Dr. Nutt, have a totally different profile, and it would be predicted that blocking norepinephrine reuptake and increasing its availability in the central and peripheral nervous system would lead to side effects such as tremor, tachycardia, and urinary hesitancy. Adverse effects caused by norepinephrine blockade have been assessed in clinical trials with reboxetine.[10] Since reboxetine has almost no affinity for serotonin and dopamine uptake sites, or for adrenergic, histaminergic, and muscarinic receptors,[2,8] the only effects expected would therefore, presumably, be due to norepinephrine reuptake inhibition.

Clinical studies showed that patients experienced only a slightly greater incidence of adverse events when given reboxetine compared with placebo (69% vs. 57%, respectively) and that the frequency of discontinuations due to adverse events was similar (< 10%) in both groups.[10] The type of adverse events experienced was partly as predicted (Figure 3). The slightly greater incidence of tachycardia compared with placebo, for example, may be due to the noradrenergic activation of β-adrenoceptors in the heart or secondary to orthostasis. Insomnia and increased sweating were also more frequent with reboxetine, effects that are most likely due to the sympathomimetic effects of norepinephrine. Dr. Nutt added that this "activating" sympathomimetic effect of reboxetine could be beneficial in patients with a classic circadian pattern of depression, since it countered the typical early morning lethargy. The higher incidence of constipation and urinary hesitancy seen with reboxetine is not due to cholinergic blockade, but rather reflects the increased levels of norepinephrine at synapses. Similarly, the dry mouth reported by some patients may be due to increased norepinephrine levels in the brain stem, leading to noradrenergic inhibition of the parasympathetic salivary output.[14]

Reboxetine had a better safety profile than imipramine, with events such as dry mouth, hypotension, tremor, and somnolence—effects characteristic of the TCAs—being experienced more frequently with imipramine than with reboxetine.[10] The comparison between reboxetine and desipramine illustrates particularly well the advantages of the selective inhibition achieved with reboxetine. Dry mouth, increased sweating, tachycardia, and blurred vision were more common with desipramine as a result of its anticholinergic effects. Hypotension was also seen more often with desipramine than with reboxetine, predictable from the α_1-adrenoceptor–blocking action of this drug (Table 2). Only urinary hesitancy was seen more frequently with reboxetine than with desipramine.

As predicted, the profile of adverse events seen with reboxetine was quite distinct from that seen with fluoxetine, but the overall frequency of adverse events was almost identical (67% vs. 65%, respectively).[10] The main adverse events seen more frequently with fluoxetine were nausea, diarrhea, and sleepiness.

Safety data from all clinical trials with reboxetine were combined to give the frequency of serious adverse events and showed that reboxetine and fluoxetine treatment had identical frequencies (0.9%), only slightly more than

seen with placebo (0.8%) and considerably less than with imipramine (2.5%).[10] Of particular interest, noted Dr. Nutt, was the fact that the frequency of serious adverse events in the elderly is lower with reboxetine treatment (2.7%) compared with imipramine treatment (7.6%). He speculated that this finding is probably due to the lower incidence of adverse effects such as hypotension. Hypotension, particularly in the elderly, is associated with falls and bone fractures and may result in a loss of confidence, severely limiting mobility and compromising quality of life. Antidepressant therapy not associated with hypotension, therefore, has particular benefit in this group of patients.

Dr. Nutt concluded by saying that inhibition of norepinephrine reuptake, as exemplified by reboxetine, is an effective and well-tolerated treatment for major depressive disorder. The additional benefits are its efficacy in severe depression and its safety in the elderly. Reboxetine therefore offers benefits to a broad spectrum of patients.

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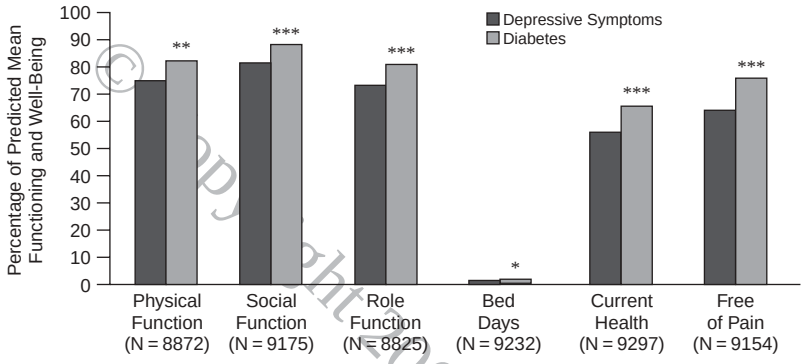
On the Mend: Quality of Remission

The impact of depression extends far beyond the easily recognized core features of depression such as depressed mood and sleeplessness, explained Dr. Schatzberg. The health, well-being, and economic status of the individual, his or her family, and society as a whole are affected. It is now clear that patients experience symptoms of depression in the periods between acute episodes and that other aspects of depression, namely social, physical, and role functioning, may be adversely affected. Even when patients are no longer classified as "depressed" according to the conventional methods of assessment, functional impairment may persist, with the patient experiencing poor quality of life during periods of remission and when the condition is untreated. Physical functionality is an obvious requirement in daily life, being necessary for self-care, household and leisure activities, mobility, and role activities. Less apparent is the requirement for social functioning. This involves more subtle "functions" such as relationships with partners, other family members, and an individual's extended social network; the ability to carry our social, family, and work roles; self-care; and leisure activities. The importance of social functioning is now well established as a clinical outcome in many psychiatric disorders, and its importance in depression has become increasingly recognized with the change from hospital- to community-based care and greater awareness of quality-of-life issues.

To illustrate this point, Dr. Schatzberg highlighted the results of a study in over 11,000 outpatients with chronic or nonchronic conditions in the United States.[1] The study found that patients with depression had worse physical, social, and role functioning than patients with no chronic physical conditions and that the functioning of patients with depression was worse than that of patients with chronic medical conditions such as diabetes, arthritis, and back complaints. The levels of well-being and functioning in patients with depression were significantly worse than for those with chronic medical conditions (e.g., diabetes; Figure 4), with the exception of chronic heart disease.

Depression affects an individual's ability to work: depressive illness is associated with difficult relationships with work colleagues and unemployment (estimated at 11% of patients with depression), and problems such as absenteeism and decreased productivity are common.[2] Functional disability at work seems to persist after the resolution of depressive symptoms. As a chronic, long-term illness, depression has far-reaching consequences

Figure 4. Well-Being and Functioning in Patients With Depressive Disorders and Those With Diabetes[a]



[a]Data from Wells et al.[1] *p < .01. **p < .005. ***p < .0001.

that can include impaired marital and family relationships, increased use of general medical services, development of coexisting disorders and the morbidity and mortality associated with those disorders, poor quality of life, and suicide.

It is now clear that many patients experience persistent depressive symptoms and significant physical, social, and role dysfunction between acute episodes. Early discontinuation of treatment following resolution of an acute episode is therefore likely to preclude full recovery. The quality of life for such patients in remission is likely to be poor. In a carefully controlled study by Coryell and coworkers,[3] the impact of unipolar affective disorder on the functioning of 240 patients with major depression was compared with that of individually matched relatives who had no history of affective disorder, over a period of 5 years. Compared with their nondepressed counterparts, patients with depression had lower rates of employment and lower likelihood of increased annual income and were more likely to never have married and twice as likely to be separated or divorced. Even in patients who recovered from the initial episode and had no further episodes in the final 2 years of follow-up, the social impairment was almost as severe as in the currently depressed patients. This was far worse than previously thought; in the words of the investigators, "the apparent consequences of affective disorder were surprisingly severe, enduring and pervasive."[3(p725)] Similarly, a 10-year follow-up study found that almost a quarter of patients experienced severe social dysfunction for greater than half the follow-up time.[4] There is additional evidence that patients with psychosis have an even greater long-term impairment of social functioning.[3]

The obvious questions are, Can treatment with antidepressants improve social dysfunction and, if this is so, does functioning improve as an aspect of improvement of depressive symptoms or is it a distinct issue? It is not known to what extent the norepinephrine or serotonin systems are implicated in social functioning. It is possible that the different classes of antidepressants may have different effects on social dysfunction and may affect particular aspects of social functioning.

Rating scales designed specifically to measure social functioning have been used in several controlled trials to examine the effects of antidepressants in alleviating social dysfunction. Dr. Schatzberg gave examples of such studies in which the benefits of antidepressant therapy on social dysfunction have been clearly demonstrated. Imipramine has been shown to be significantly more effective than placebo in improving social functioning in adults with dysthymia, as measured using the Social Adjustment Scale-Self Report (SAS-SR).[5] Similarly, in another study,[6] patients with chronic depression were treated with either sertraline or imipramine for 12 weeks. The social functioning of the groups was also compared with that of the community "norm." There was no significant difference between the 2 treatments as assessed using the SAS-SR, but treatment with either was found to alleviate severe psychosocial impairment, particularly in patients who achieved remission, with the level of social functioning approaching that of the community sample.

Some studies have also compared TCAs with SSRIs, but so far there is no conclusive evidence that one is better than the other in improving social functioning. There is, however, some evidence that the inhibition of norepinephrine reuptake, rather than serotonin reuptake inhibition, may have a greater effect on improving social functioning. A relatively new rating instrument, the Social Adaptation Self-evaluation Scale (SASS),[7] was used to assess improvement in patients treated with fluoxetine or reboxetine for 8 weeks. Reboxetine was associated with a significantly greater improvement than fluoxetine (or placebo) in the social functioning of the patients.

Depressive illness has an impact on all aspects of a patient's life, including interactions with family, friends, and work colleagues. Treating the symptoms of depression during acute episodes is simply not sufficient. Physicians need to be aware that even after the core symptoms of depression have been resolved, there is still a need to

continue therapy to prevent relapse and recurrence, which may even improve quality of life. It may even be the case that social functioning should be the prime target of antidepressant therapy. It is currently unclear whether antidepressants have differential effects and to what extent these effects can be explained in terms of pharmacology, thus presenting a considerable challenge to the physician in prescribing appropriate treatment.

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Social Integration of the Depressed Patient

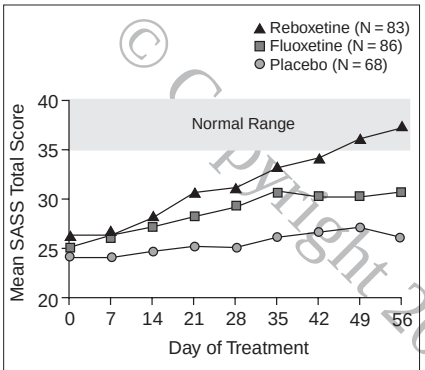
Social functioning has a major impact on quality of life in patients with depression. Until recently, however, the effect of antidepressant therapy on impaired social functioning has received less attention than symptom relief. Currently available antidepressants, including the TCAs, SSRIs, and the new selective NRI, reboxetine, have demonstrated efficacy in improving the symptoms of depression in a variety of patient groups. To date, there is no regulatory requirement to show efficacy with regard to improving social functioning. Consequently, less is known about the relative efficacy of antidepressant drugs with regard to social functioning compared with relief of symptoms. Professor Kasper focused on the clinical evidence available to the physician wanting to choose the most appropriate antidepressant for patients with social impairment. Social functioning, he explained, is an individual's ability to fulfill his or her everyday roles as, for example, a spouse or parent. When these roles are not fulfilled to expectation or satisfaction, then the family, social circle, and work performance of the individual are affected. There are economic implications due to lost working days and reduced productivity. The severity of depressive symptoms and that of social impairment are not necessarily comparable and do not necessarily improve at the same rate. Social dysfunction should be regarded as playing a major role in depression, and these parameters need to be measured independent of symptom parameters to assess fully the response to treatment.

Some studies have shown that pharmacotherapy is effective in treating social dysfunction. One study comparing fluoxetine (20–40 mg/day) with clomipramine (75–150 mg/day) and amitriptyline (50–100 mg/day) in patients with depression found that, despite the fact that there were no significant differences between treatments in improvement in symptom severity, there were significant differences in the quality of life reported by patients.[1] Both of the TCAs were significantly more effective than fluoxetine in improving the general health perception and social functioning of patients. This, said Professor Kasper, suggested that there may be differences in the pharmacologic mechanism of action of antidepressants that were responsible for alleviating social impairment.

Another study compared sertraline (up to 200 mg/day), imipramine (up to 300 mg/day), and placebo in a 12-week study in patients with dysthymia.[2] Both sertraline and imipramine were significantly more effective than placebo in improving the symptoms of depression, as measured by the Clinical Global Impressions scale. The investigators also used several quality-of-life instruments to assess social functioning, including the SAS-SR, the Global Assessment of Functioning, the Longitudinal Interval Follow-up Evaluation (LIFE), and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). All ratings concurred in showing that both antidepressants were also more effective than placebo in improving social functioning in these patients. Miller and colleagues[3] studied the same drugs in patients with chronic major depression or double depression, using the LIFE, the SAS-SR, the 36-item Short Form, and the Q-LES-Q. After 8 weeks, both active treatments had improved social functioning, although neither group of patients achieved "normal" levels of functioning by the end of the study.

Two 8-week studies have been conducted to compare the efficacy of reboxetine with that of the SSRI fluoxetine in relieving symptoms of both depression and social impairment in patients with major depressive disorder. In one study,[4] which was also placebo controlled, the improvement in HAM-D score was similar with the active treatments (reboxetine and fluoxetine); both were significantly more effective than placebo but not significantly different from one another. The number of patients who responded to treatment was the same in

Figure 5. Mean SASS Total Scores Over Time (total study population) for Reboxetine (8–10 mg/day), Fluoxetine (20–40 mg/day), and Placebo[a]



[a]Reprinted, with permission, from Dubini et al.[5]
Abbreviation: SASS = Social Adaptation Self-evaluation Scale. $p < .05$, reboxetine and fluoxetine vs. placebo from day 7; $p < .05$, reboxetine vs. fluoxetine from day 42.

each active-treatment group (56%), while slightly more patients taking reboxetine achieved remission compared with those taking fluoxetine (47.6% vs. 45.2%). However, a marked between-treatment difference was observed in mean SASS social functioning score. Reboxetine was significantly more effective than placebo from day 7 of treatment and significantly more effective than fluoxetine from day 42 onward (Figure 5). By the end of the study, added Professor Kasper, of the 3 treatment groups, only the reboxetine group had a mean SASS score that was in the range defined as "normal." In the subset of patients in symptomatic remission by the last assessment, reboxetine was associated with significantly higher SASS scores than placebo by day 28 and fluoxetine by day 35.

The second (non–placebo-controlled) study[6] had shown similar results, reported Professor Kasper. Again, the improvement in depressive symptoms was comparable in the reboxetine and fluoxetine groups, but the improvement in the mean SASS total score was 42.4% in the reboxetine-treated group, compared with 33.3% in the fluoxetine-treated group, for patients treated for at least 4 weeks. In the cohort of patients in remission, the improvement in social functioning with reboxetine was significantly better than with fluoxetine. When the subgroup of patients who eventually achieved remission was considered, there was a significantly greater improvement in the SASS score of patients treated with reboxetine, compared with those treated with fluoxetine (56.5% vs. 37.8%, respectively; $p < .05$).

The results of these 2 studies show that reboxetine treatment improves social functioning while still maintaining effective symptom relief. From the patients' viewpoint, this may encourage good medication compliance, which in turn leads to a reduced probability of relapse or recurrence. Even when a patient is assessed as "in remission" using the HAM-D or another rating scale, there are often still signs of impaired social functioning. This impairment can have an impact on the patient's quality of life.[4] The issue of social functioning needs to be considered when prescribing antidepressants, since it is just as important to be able to restore the individual's ability to interact with his or her environment as to relieve the symptoms of depression.

In referring back to the current understanding of the serotonin and norepinephrine pathways involved in depression, Professor Kasper noted that although the neurophysiologic mechanisms involved in social functioning are poorly understood, these studies suggested that the norepinephrine pathway may play a greater role.

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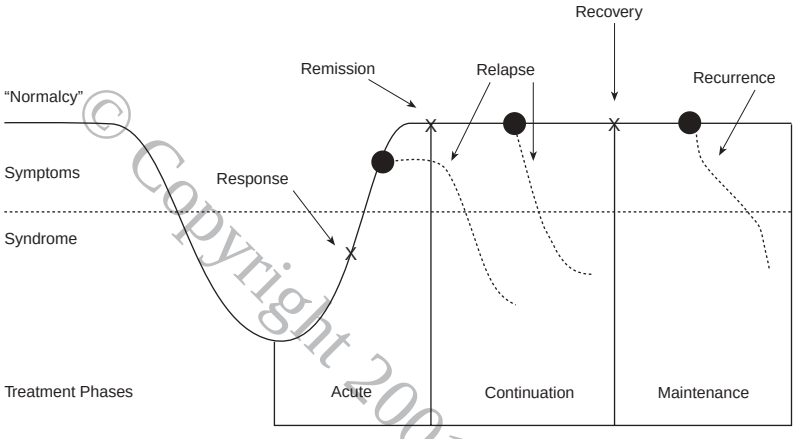
Preventing the Long-Term Complications of Depression

Ensuring complete recovery and implementing preventive therapy are essential to the long-term well-being and optimal functioning of patients, stated Dr. Thase. Recurrent depression is common, disabling, and potentially life-threatening, and it has an impact on family, social circle, and work relationships. Despite an apparent recovery from an episode of depression, people continue to experience psychosocial impairment, which may persist for up to 5 years.[1] Perhaps the most troublesome fact is that the risk of suicide is increased, compared with the rest of the population, for at least 3 years following an acute depressive episode. The risk of recurrence is high, with recurrence within 1 year being estimated at 33%, within 5 years at 50%, and within a lifetime at greater than 70%.[2] In other words, the cumulative probability of recurrence increases with the time elapsed following an episode.

The risk of future depression also increases progressively with each recurrence; people who have experi-

Figure 6. The Course of Depression[a]



[a]Adapted, with permission, from Kupfer.[8]

enced 2 prior depressive episodes have an estimated 80% risk of recurrence, while those who have experienced 3 prior episodes have a 90% risk. This has raised the question of whether depression is "kindled,"[3] i.e., whether pathophysiologic changes associated with depression cause changes in the brain stress-response mechanisms that compromise the ability to cope with the next stressful episode. In this way, progressively less stress or provocation would be required to precipitate subsequent episodes.

Other risk factors include recent remission and dysthymia. Age at onset appears to be an important factor: people experiencing their first depressive episode before the age of 21 years or after the age of 60 years appear to be at greater risk of developing recurrent depression. Women may also be at greater risk. It has been estimated that between 10% and 20% of patients with recurrent depression have a seasonal (fall-winter) pattern, possibly precipitated by sensitivity to the drop in daily light exposure.[4] Comorbidity and stressful events contribute to the probability of depression, although the ability to cope with such situations varies. Certain personality types may be more prone to depression, for example, those with a tendency to neuroticism (i.e., people who are emotionally more vulnerable and more reactive to stress). Poor levels of social support and low self-confidence in acquiring social support are also believed to be predictive of depression and to prolong its course.[5–7]

The time course of recovery from depression is typically depicted as a progression of distinct phases (Figure 6).[8] A response to acute pharmacotherapy is expected within 4 to 6 weeks, with a further 4 to 6 weeks possibly being necessary to consolidate this response and ensure that no further dosage adjustments are required. Typically, when the acute episode has been successfully treated and the patient is deemed to be in remission, treatment is "thinned," with fewer treatment sessions. The continuation phase is generally a minimum of 4 months but may extend to up to 12 months. The risk of relapse, i.e., a "resurfacing" of the same depressive episode, is estimated at 40% to 60% if an antidepressant is discontinued within the first few months of response, irrespective of the class of antidepressant, but this is reduced to a risk of 5% to 10% with continuation therapy.[9,10] Psychotherapy may be continued or even added during this continuation period to address ongoing interpersonal difficulties. The subsequent maintenance phase is implemented to reduce the risk of recurrence, a term used to define the onset of an entirely new episode of depression.

Categorization into phases may be misleading. In reality, recovery can be a much slower process, with the patient remaining vulnerable to recurrence for months or even years. Continuation pharmacotherapy is warranted for virtually all responders, and its importance cannot be overemphasized.

There are also risk factors associated with relapse. For example, biochemical measurements have revealed that hyperactivity of the hypothalamic-pituitary-adrenal (HPA) cortical axis is a marker of potential relapse.[11] Stress responses in the HPA axis, as well as serotonergic and noradrenergic neuromodulatory systems, are thought to be poorly regulated in patients at risk of relapse. One view of treatment is that it may dampen or normalize these overreactive stress response systems, therefore reducing the risk of relapse.

One study clearly illustrated the benefits of maintenance therapy.[12] This study was performed in outpatients with highly recurrent unipolar depression and comprised a 3-year randomized trial to assess the prophylactic efficacy of imipramine, interpersonal psychotherapy (IPT), and a combination of the 2 approaches. Patients who were in recovery from at a minimum their third episode of major depression were admitted to the study. All 128 patients included in the study had been successfully treated with imipramine and IPT and remained free from depression for 4 months of continuation therapy. The patients were randomly assigned to 1 of 5 maintenance regimens as follows: (1) maintenance IPT (IPT-M), (2) IPT-M with imipramine,

(3) IPT-M with placebo, (4) imipramine, and (5) placebo. Patients who received maintenance therapy comprising monthly IPT alone (group 1) or with placebo (group 3) had an 18% and 31% chance of remaining well for the 3-year period, respectively, whereas patients who received no maintenance therapy (group 5) had the worst outcome with only a 9% chance of remaining well within the 3-year period. Psychotherapy alone (group 1) and with placebo (group 3) significantly delayed the onset of the recurrent episode of depression by a number of weeks (group 1, 51 weeks; group 3, 61 weeks) when compared with placebo alone (group 5, 21 weeks). However, patients who received active pharmacotherapy had the greatest chance of remaining well throughout the study. A 3-year survival rate of 46% was reported in those patients treated with imipramine alone (group 4) compared with 60% in the IPT-plus-imipramine group (group 2). The study clearly showed that maintenance with an antidepressant was the most beneficial prophylactic approach. When such medication was not given, psychotherapy was of some benefit.

Another study was conducted in patients with chronic depression (pure dysthymia, double depression, or chronic major depression according to DSM-III-R).[13] Patients who were in remission after treatment with desipramine were randomly assigned to continue treatment with desipramine or be tapered to placebo for a maintenance period of 2 years. The relapse rate was approximately 50% in the placebo group and 10% in the desipramine group.

Maintenance therapy has also proved beneficial in treating atypical depression. A 26-week maintenance study in patients with atypical depression (characterized by overeating, oversleeping, and preserved mood reactivity) found that the MAOI phenelzine had a strong prophylactic effect in patients who had been stabilized on treatment with the same drug, whereas discontinuation within 6 months after improvement resulted in a high risk of recurrence (approximately 90%).[14] The same study also looked at the rates of relapse in patients who were stabilized on imipramine treatment. The recurrence rate for patients who were maintained on imipramine treatment was about the same as for those who were switched to placebo (approximately 50%). It is interesting, however, that patients who discontinued phenelzine had a greater risk of recurrence than the patients who discontinued imipramine. The results suggest that an antidepressant with a vigorous acute phase response, such as phenelzine, may be associated with a more rapid loss of effect on withdrawal.

There is a pervasive view among physicians that SSRIs do not have the sustained efficacy required for long-term treatment. This view is not necessarily justified, however. Dr. Thase gave some examples of clinical trials in which this view was disproved, e.g., a double-blind, placebo-controlled study performed in 480 patients with major depressive disorder.[15] All patients were administered sertraline for 8 weeks, after which patients were randomly assigned to receive either sertraline or placebo for a further 44 weeks. While almost 46% of patients receiving placebo had relapsed by the end of this time, only 13% of the patients receiving sertraline had relapsed. Another double-blind randomized trial found a clearly maintained effect with paroxetine over a 12-month period.[16] A relapse rate of 16% was seen with the SSRI, compared with a rate of 43% in the group receiving placebo. Similarly, a study comparing fluvoxamine with sertraline[17] found that both medications maintained a response in approximately 85% of patients over a period of 25 months.

A study by Stewart and coworkers[18] suggests a reason for the perception among physicians that they are observing a high rate of "breakthrough" episodes with SSRIs. The study compared fluoxetine treatment with placebo over 62 weeks. Patients who responded to acute-phase treatment had treatment discontinued after 12, 26, or 50 weeks. Overall, the rate of relapse was always lower in the groups treated with active medication compared with placebo. However, among the subgroup of patients who had an acute phase response suggestive of placebo (i.e., a rapid, fluctuating, or inconsistent course of symptomatic improvement), fluoxetine did not have a significantly greater preventive effect than placebo. Dr. Thase suggested that a possible explanation for the apparent "breakthrough" effect is that the newer, safer antidepressants are better tolerated and therefore patients stay on treatment for longer periods of time. Additionally, clinicians are more willing to prescribe antidepressants for longer periods. Thus, we are now seeing patients who are apparently failing after some time on successful treatment. In fact, what we may be seeing is patients who had initially responded to the placebo effect of the treatment, which then begins to fail as the interpersonal contact diminishes during long-term treatment. This theory needs testing in long-term treatment, i.e., 3- to 5-year studies. The other major possible cause of the apparent decrease of medication effect is, of course, poor compliance on the part of the patient.

Preliminary data on maintenance therapy with the newer antidepressants bupropion, venlafaxine, nefazodone, mirtazapine, and reboxetine are now available. Dr. Thase concentrated on the reboxetine data, describing the results of a yearlong, placebo-controlled study.[19] Patients who responded to 6 weeks of treatment with reboxetine were randomly assigned to continue on reboxetine, 8 mg/day, or to switch to placebo. The relapse rate was significantly ($p < .001$) lower with rebox-

etine treatment than with placebo (22% vs. 56%, respectively). After 12 months, 78% of patients treated with reboxetine were in remission, compared with only 45% of those maintained with placebo ($p < .001$). In addition, reboxetine was well tolerated: the frequency of adverse events was only slightly higher in the reboxetine group compared with the placebo group (28% vs. 23%, respectively), and discontinuations due to adverse events were low in both groups (4% vs. 1%, respectively).

Dr. Thase focused on a couple of common misconceptions concerning maintenance therapy. It is often the case that the antidepressant dosage is reduced in long-term therapy, when, for example, the patient encounters adverse side effects or becomes ambivalent about his or her need for continued therapy. However, such reduction is to be avoided. There is clinical evidence with imipramine that halving the dosage results in a significant risk of reducing the efficacy in maintenance therapy,[20] particularly in those patients who have experienced several recurrences. Whether this is the case for the newer antidepressants has yet to be tested. When the patient and physician decide that antidepressant therapy can be stopped—and this should be done on an individual basis—it should be tapered slowly. Another possible mistake is to withdraw or taper the maintenance therapy too soon. Traditionally, patients are continued for 2 cycles, which may require 4 to 6 years of therapy, based on the patient's history. However, it is becoming increasingly recognized that this length of time may be insufficient. In a small study conducted by Kupfer and coworkers,[21] patients without recurrence after 3.5 years of treatment with imipramine were randomly assigned to continue for a further 2 years on full-dose maintenance therapy or to switch to placebo, in a double-blind fashion. Although the number of patients was small, a clear difference in recurrence rates was seen, with only 5% of patients in the imipramine group experiencing recurrence compared with almost 70% in the placebo group. It appears that even 3.5 years of antidepressant therapy was inadequate to prevent a subsequent recurrence in these patients after withdrawal of maintenance therapy.

Prophylactic therapy may be required for long periods of time, and because of this, the frequency and type of side effects associated with treatment are important. When tricyclics were the predominant treatment, the problem of side effects was such a key issue that other types of therapy were used. There is a trend in Europe to use lithium for long-term prevention. There is evidence for lithium's preventive efficacy, and it may be considered if long-term antidepressant therapy fails. Newer anticonvulsant mood stabilizers may also have a role to play in this type of therapy, but their efficacy is as yet unproved. Prevention of relapse after successful electroconvulsive therapy is a necessity, often requiring multiple drug therapy with mood stabilizers and antidepressants. The use of psychotherapy and psychoeducation—educating the patient, and his or her family when possible, on key issues of the illness and the importance of long-term therapy—is also likely to be beneficial.

Long-term therapy raises particular concerns regarding unwanted side effects not necessarily seen or so deleterious during short-term therapy. These include weight gain, constipation, and dental caries (caused by chronic xerostomia), which occur with many agents; sexual dysfunction (seen with the SSRIs, TCAs, and MAOIs); and weight gain, acne, diarrhea, polyuria, tremor, and hypothyroidism, which can all complicate long-term lithium-therapy.[2]

In summary, maintenance therapy at full dose is recommended for all patients perceived to be at an unacceptable risk of recurrent depression. In clinical terms, this applies, for example, to patients who have had 3 or more episodes, or 2 episodes within 3 years, and to patients who have had an episode of depression in which they have attempted suicide. Both physicians and patients need to be aware of the benefits of maintenance therapy and the serious detrimental effects of noncompliance. An indefinite duration of treatment may also be necessary in patients at high risk of recurrent depression.

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To cite a section from these symposia, follow the format below:
Nutt DJ. The medicine: current treatment advances in depression, pp 382–385. In: Montgomery SA, chair. Understanding Depression: A Long-Term, Recurring Disorder (ACADEMIC HIGHLIGHTS). J Clin Psychiatry 2001;62:379–392