Can Long-Term Treatment With Antidepressant Drugs Worsen the Course of Depression?

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Background: The possibility that antidepressant drugs, while effectively treating depression, may worsen its course has received inadequate attention.

Method: A review of the literature suggesting potential depressogenic effects of long-term treatment with antidepressant drugs was performed. A MEDLINE search was conducted using the keywords *tolerance, sensitization, antidepressive agents,* and *switching*. This was supplemented by a manual search of Index Medicus under the heading "antidepressant agents" and a manual search of the literature for articles pointing to paradoxical effects of antidepressants.

Results: A number of reported clinical findings point to the following possibilities: very unfavorable long-term outcome of major depression treated by pharmacologic means, paradoxical (depression-inducing) effects of antidepressant drugs in some patients with mood and anxiety disturbances, antidepressant-induced switching and cycle acceleration in bipolar disorder, occurrence of tolerance to the effects of antidepressants during long-term treatment, onset of resistance upon rechallenge with the same antidepressant drug in a few patients, and withdrawal syndromes following discontinuation of mood-elevating drugs. These phenomena in susceptible individuals may be explained on the basis of the oppositional model of tolerance. Continued drug treatment may recruit processes that oppose the initial acute effects of a drug and may result in loss of clinical effect. When drug treatment ends, these processes may operate unopposed, at least for some time, and increase vulnerability to relapse.

Conclusion: The possibility that antidepressant drugs may worsen the course of depression needs to be tested, even though its scientific exploration is likely to encounter considerable methodological and ideological difficulties. The clinical implications of this hypothesis in depression are considerable. Antidepressant drugs are crucial in the treatment of major depressive episodes. However, appraisal of paradoxical effects that may occur in susceptible patients during long-term treatment may lead to more effective use of the drugs.

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Awareness of the bleak long-term outcome of depression in terms of relapse and recurrence is increasing.[1–3] This awareness is leading to the conceptualization of depression as a chronic disease, with the resulting need of endorsing treatment protocols such as those used for diabetes.[4] Major depression has been ranked as the fourth most disabling medical disorder by disability-adjusted life-years, a measure of burden.[5] By 2010, major depression will be ranked second unless meaningful improvements occur in prevention, diagnosis, and treatment.[5]

A paradox has emerged: physicians are more and more likely to diagnose and treat depression, and treatments have become more and more refined.[6] But this, in a long-term perspective, does not seem to matter much.[4] Several explanations have been proposed for this paradoxical phenomenon. The poor outcome among depression patients may reflect the inadequate treatment that patients tend to receive in general practice, in terms of dose or length of treatment; their poor compliance; and the complications of medical comorbidity.[7–9]

However, poor outcome also occurs in psychiatric settings,[1–4,10] and, in primary care, outcome does not seem to be affected by enhanced acute-phase treatment.[11] It may reflect the partial nature, even in specialized centers, of current treatment modalities, which leave substantial residual symptomatology, probably the most powerful predictor of subsequent relapse.[12] Patients relapse simply because they have never fully recovered. Relapse may be due to the loss of nonspecific placebo effects rather than to true drug effects.[13] The most common conviction among researchers and clinicians has probably been the recognition of the chronic nature and increasing incidence of depres-

sive illness.[4] However, we seem to forget and do not want to entertain another possibility: the likelihood that antidepressant drugs may be depressogenic, at least in some cases.[14]

In clinical medicine, the likelihood that a specific treatment, while alleviating the symptoms of disease, may aggravate its course, has often been evaluated. In central nervous system diseases, the possibility that early treatment of Parkinson's disease with levodopa may worsen its progression has been discussed.[15] Similar concerns have been raised with the long-term treatment of asthma with inhaled β-agonists,[16] which have been associated with tolerance[17] because of the loss of bronchodilator effect with time. Another issue that is currently debated is the role of hormone replacement therapy in the pathogenesis of heart disease in postmenopausal women.[18] Obviously, these problems are difficult and complex to study, and definitive answers may be unavailable. Nonetheless, these questions are always worth asking, at least for a better understanding of some side effects of therapy and of therapeutic choices.

The possibility that antidepressant drugs might unfavorably affect the outcome of depression was formulated in a specific hypothesis only fairly recently, in 1994.[19] It was suggested that long-term use of antidepressant drugs may increase, in some cases, biochemical vulnerability to depression and worsen the long-term outcome and symptomatic expression of the illness, decreasing both the likelihood of subsequent response to pharmacologic treatment and the duration of symptom-free periods. This largely speculative hypothesis was subsequently extended to the risks and implications of interrupting maintenance psychotropic drug therapy[20] and developed in neurobiological terms.[21,22]

The aim of this article is to update and complete the original tentative formulation[19] by reviewing the clinical literature that may suggest that antidepressant drugs worsen the course of depression and by discussing the neurobiological framework for such events. A MEDLINE search of the literature, using *tolerance, sensitization, antidepressive agents,* and *switching* as keywords, was performed. This search was supplemented by a manual search of Index Medicus under the heading of "antidepressive agents." Further, a manual search of the psychiatric literature was performed to locate articles that point to paradoxical effects of antidepressant drugs. The results of this search are presented in this article and examined under the light of a unifying hypothesis, together with some suggestions for further research in this neglected area. The findings of this selective search call for a more cautious attitude among clinicians in prescribing antidepressant drugs.

A number of clinical observations scattered in the psychiatric literature provide a ground for postulating that—at least in some patients—antidepressant drugs may worsen the course of depression. Many of these data derive from uncontrolled clinical observations and bear limited implications if considered on their own, but achieve meaning and raise important questions if they are examined in the light of a unifying hypothesis.

CLINICAL PHENOMENA THAT MAY BE LINKED TO THE OCCURRENCE OF SENSITIZING EFFECTS OF ANTIDEPRESSANT DRUGS

Poor Long-Term Outcome of Major Depression Treated by Pharmacologic Means

There is evidence that casts some doubt on the ability of antidepressant drugs to favorably affect the course of depressive illness, despite their recognized ability to treat the depressive episode. Viguera et al.[23] analyzed 27 studies with variable length of antidepressant treatment that reported follow-up at drug discontinuation. Duration of drug treatment did not seem to affect long-term prognosis once the drug was discontinued. Whether one treats a depressed patient for 3 months or 3 years, it does not matter when one stops the drugs. A statistical trend suggested that the longer the drug treatment, the higher the likelihood of relapse.[23] In a subsequent analysis[24] including another study,[25] risk of post-discontinuation relapse was nearly significantly greater after long treatment following recovery from an index episode of major depression ($\rho = 0.37$; $p = .052$). In a naturalistic, prospective study,[26] low doses of antidepressants appeared to be less beneficial than either higher doses or clinical management without antidepressant drugs. The latter 2 treatments yielded almost identical outcome.

An observational study of 236 unipolar patients, who had received antidepressants during recovery and were followed for an affective recurrence for up to 5 years, showed that the rate of recurrence for patients with fewer than 5 previous episodes was not affected by medication after the initial 8 months.[27] Patients who had experienced more than several recurrences were at a greater risk of recurrence and continued to benefit from any level of medication during the first year after recovery. A large double-blind, placebo-controlled study[28] of the optimal duration of antidepressant treatment found a significant protective effect of fluoxetine compared with placebo as to relapse rate after 24 weeks of treatment (26% for fluoxetine and 48% for placebo), but not after 62 weeks (11% for fluoxetine and 16% for placebo). Both studies indicate that antidepressant drugs generally fail to protect after 6 months of treatment, but do not imply that antidepressant drugs may worsen the natural course of depression. Furthermore, in naturalistic studies,[26,27] we cannot be sure about the compliance of patients.

Stassen et al.[29] found that the time course of improvement among responders to amitriptyline, oxaprotiline, and placebo was independent of the treatment modality and thus identical in all 3 groups. Once triggered, the time

course of recovery from illness became identical to the spontaneous remission observed with placebo. Antidepressants, therefore, may not change the pattern of the natural course of recovery from depression, but simply speed the recovery and change the boundary between "responders" and "nonresponders."[29] Baldwin[30] observed that, after drug treatment, about one quarter of patients with major depression in later life remain symptom-free, one third experience at least 1 relapse but experience further recovery, and the remainder have residual symptoms. In about 10% of all cases, depressive symptoms remain severe and intractable. These proportions appear to have altered little since antidepressant drugs became available.[30]

The literature thus indicates that antidepressant drugs are effective in preventing recurrences while they are being administered[31] and do not yield a protective effect once they are discontinued. The correlation between duration of antidepressant drug treatment and likelihood of relapse on discontinuation may suggest that it is not simply a matter of failure to protect, but that a neurobiological mechanism increasing vulnerability may be involved.

Paradoxical Effects of Antidepressant Drugs

In 1968, Di Mascio et al.[32] studied the effects of imipramine on individuals who varied in levels of depression, using a double-blind, placebo-controlled procedure. They found an increase in depression levels after the use of imipramine in the subjects with the lowest scores of depression. A few years later, Van Scheyen[33] performed a naturalistic follow-up study of 56 female and 28 male patients with recurrent vital depression. At a time when antidepressant drugs were not as widely prescribed as they are today, the author observed that systematic treatment with tricyclic antidepressants proved to be associated with an increase in the total number of recurrences, which attained statistical significance in female patients. Van Scheyen wondered "whether such an increased number of depressive phases would not be regarded as a side effect or paradoxical effect which, after protracted therapy, is produced by the tricyclic antidepressants so far most commonly used."[33(p110)] Patients, however, were not randomly assigned to treatment with antidepressant drugs, and the author's observation may have reflected the more severe characteristics of illness of those patients who were judged to be in need of antidepressant drugs. More recently, in the course of a randomized, double-blind crossover study comparing the effects of reboxetine and sertraline in 20 healthy volunteers,[34] 2 subjects reported becoming depressed and another 2 reported becoming suicidal.

Similar observations have been made with treatment of anxiety disorders by antidepressant drugs. Commenting on the development of endogenous depression in patients with panic disorder treated with therapeutic doses of antidepressants, Aronson[35] suggested the possibility that antidepressant medications may unmask a depressive diathesis. Fux et al.[36] observed the emergence of depressive symptoms in 7 (9%) of 80 patients during the treatment of panic disorder with fluvoxamine. These patients had no history of mood disorder, and no symptoms of depression were present before treatment with fluvoxamine. The symptoms abated when fluvoxamine was discontinued and a tricyclic antidepressant or clonazepam was prescribed, and they reappeared when fluoxetine was administered. Fux et al.[36] suggest the possibility of a vulnerability among some panic disorder patients to a noradrenergic-serotonergic imbalance caused by selective serotonin reuptake inhibitors (SSRIs).

The question that arises is whether such paradoxical phenomena may affect only a few individuals or are manifestations of a subtle, but general effect. The results of a recent randomized controlled trial comparing cognitive-behavioral therapy (CBT), imipramine, or their combination for panic disorder[37] point to the possibility of a general effect in panic disorder. Six months after treatment discontinuation, response rates were 41% for CBT plus placebo, compared with 26% for CBT combined with imipramine. A relationship between use of antidepressant drugs and increased relapse risk of panic disorder has been reported by other investigators,[38–40] and depression was found to occur during the follow-up of patients receiving tricyclic antidepressants for panic disorder.[41] Another intriguing phenomenon involves the concept of a therapeutic window, which was originally applied to nortriptyline,[42] but was subsequently described with SSRI therapy.[43–47] The possibility of paradoxical or no effects occurring above a certain dosage would be in line with the phenomena described with patients with affective disorders and healthy controls. In any event, these effects appear to occur in a very limited percentage of patients treated with antidepressants.

Antidepressant-Induced Switching in Bipolar Disorder

The occurrence of mania in depressed patients upon treatment with antidepressant drugs is a relatively old clinical observation. A switch into mania is frequent in patients with bipolar disorder, even if they are treated with a mood stabilizer. Post et al.[48] have estimated that antidepressants may double the incidence of a switch (50% of cases) compared with placebo (25% of cases). Such incidence may be even higher in rapid-cycling bipolar disorder.[48] In a study that reviewed the experience over 6 decades in the author's clinic, Angst[49] presented evidence that can be interpreted as consistent with drug-induced cycling as distinct from spontaneous cycling. In the early 1980s, Kukopulos et al.[50,51] observed how treatment by antidepressant drugs may contribute to changes of course from unipolar to bipolar illness and to an increased frequence of cyclicity. Cycle acceleration has been subsequently confirmed by other investigators.[48]

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Kukopulos et al.[50,51] deserve credit in raising the possibility that antidepressant-induced mania is not simply a temporary and fully reversible phenomenon, but may trigger complex biochemical mechanisms of illness deterioration. A case of tricyclic-induced mania in a 60-year-old woman with a long-standing history of unipolar depression (that was followed by rapid cycling refractory to lithium) illustrates the hormonal implications of such mechanisms.[52]

Despite initial denial, the view that use of antidepressant drugs may worsen the course of bipolar disorder has achieved wide currency.[48] However, the possibility that antidepressant drugs may induce episode acceleration in unipolar depression has not been adequately studied. Goodwin[53] has illustrated how this could occur. If both depressive and manic episodes tend naturally to evolve toward remission (into either a euthymic phase or an episode of opposite polarity) and antidepressant drugs accelerate this natural tendency, drug treatment may accelerate the next sequence in the natural course (i.e., the onset of a manic episode instead of euthymia). According to Goodwin, "If the natural sequence of recurrent unipolar illness goes from depression to recovery and then eventually to the next episode, treatments that accelerate recovery of the index depression could also accelerate the onset of the next episode."[53(p43)]

Tolerance to Antidepressant Drugs

The return of depressive symptoms during maintenance antidepressant treatment was found to occur in 9% to 57% of patients in published trials.[54] Possible explanations include pharmacologic tolerance, loss of placebo effect, increase in disease severity, change in disease pathogenesis, accumulation of a detrimental metabolite, unrecognized rapid cycling, and prophylactic inefficacy.[54]

Several clinical observations point to the existence of tolerance phenomena during antidepressant treatment.[24,55] Some data point to dispositional (pharmacokinetic) tolerance, which reduces the concentration of a drug. For instance, patients who relapsed while on fluoxetine treatment (20 mg/day) responded to an increased dosage of the same drug (40 mg/day).[56] Other studies, however, suggest the likelihood of pharmacodynamic processes that change sensitivity to the drug. Mann[57] observed loss of antidepressant effect with long-term monoamine oxidase (MAO) inhibitor treatment without loss of MAO inhibition. Lieb and Balter[58] described the development of tolerance to antidepressant effects that was refractory to dosage increase.

The effectiveness of dose increase for relapse during maintenance treatment of major depression was assessed in a recent study of fluoxetine administered as a 20-mg daily or an enteric-coated 90-mg weekly dose.[25] Patients on treatment with fluoxetine, 20 mg/day, had their dose increased to 40 mg/day, and those taking a 90-mg weekly dose had their dose increased to 90 mg twice a week. Fifty-seven percent of the patients in the 40-mg daily group and 72% of the patients in the 90-mg twice weekly group responded to the dose increase. One patient in 5 who initially responded to dose increase relapsed again during the 25-week trial.[25] It is conceivable that this proportion would have increased with continuation of the trial, as was found to be the case in recurrent depression.[59] These data, therefore, strongly point to pharmacodynamic tolerance.

One should also pay attention, however, to the percentage of patients who do not display a loss of therapeutic effect during maintenance treatment (for instance, the 82% of patients who stayed well against the 18% of patients who relapsed while taking full-dose imipramine during the 3-year Pittsburgh Maintenance Study[60]). The phenomena subsumed under the rubric of tolerance in mood disorder bear strong resemblances to the progressive losses of effect that have been observed with both antidepressant and antianxiety drugs in anxiety disorders.[61] These phenomena have also been classified as fading (progressive decrease of therapeutic effects refractory to dosage increase, after non-immediate symptomatic improvement).[62]

Resistance to Antidepressant Drugs

There is considerable confusion about the term *resistance* in mood disorder. An important distinction is whether the term is applied to depressive illness (an episode that does not respond to drugs or psychotherapy) or to antidepressant drug therapy (a drug that resulted in clinical response is no longer effective when it is started again after a drug-free period). The former use of the term is the prevalent one, but the latter is also worthy of clinical attention.

In 1984, Lieb and Balter[58] described the resistance of some patients to antidepressant drugs that had previously been effective. Change to another antidepressant drug yielded clinical benefits, but was followed by refractoriness as well. Ten years later, similar phenomena were described and related to long-term low-dose antidepressant treatment.[19] Lieb and Balter[58] considered this resistance to be an example of tachyphylaxis (the increasing tolerance to a drug that develops following repeated administration).

It has repeatedly been observed[63–65] that bipolar patients who respond well to lithium do not always regain the same degree of initial responsiveness with lithium reinstitution. This, however, may indicate the progression of the illness and not a drug-related phenomenon. Indeed, a large naturalistic follow-up of patients with affective disorders failed to provide evidence that lithium discontinuation results in treatment resistance when lithium treatment is resumed.[66] In a 6-year outcome study of unipolar depression,[67] patients who relapsed while drug free were prescribed the same antidepressant that was effective in the initial episode. Resistance occurred in 4% of cases. Friedman et al.[68] observed onset of resistance after reinsti-

tution of desipramine treatment in 1 of 12 patients with dysthymia who had relapsed after being switched to placebo. Donaldson[69] described 3 patients with major depression who relapsed while on phenelzine treatment and developed a severe chronic depression that was refractory to other treatments. The phenomenon of resistance was analyzed in a study of 122 patients who, after initially responding to fluoxetine, were assigned to placebo. About half of the patients relapsed. After reinitiation of medication, 38% of the patients either did not respond or initially responded but again relapsed.[70] Similar results were obtained after discontinuation of an SSRI in obsessive-compulsive disorder.[71]

The few data available thus indicate that when drug treatment is reinstituted, the patient may not respond to the same antidepressant that improved depressive symptoms the first time. The prevalence of this resistance that ensues varies. Patients who respond to reinstitution of the same antidepressant drug may display a subsequent loss of therapeutic effect.[70] This suggests that resistance and loss of clinical effects may be related and share a common mechanism. Episodes that are simply classified as responding poorly to antidepressant drugs[72] may underlie the phenomena described here (previous successful response to antidepressant drugs). This issue is currently neglected, but it is worthy of research attention.

Withdrawal and Dependence

Withdrawal symptoms following discontinuation of treatment with antidepressants were soon recognized after the introduction of these drugs.[73] They have been described with all types of antidepressant drugs,[74] and particularly with MAO inhibitors and SSRIs.[75–79] One of the first potential explanations involved a cholinergic rebound, yet this hypothesis is unlikely to explain serotonergically mediated withdrawal syndromes of SSRIs.[80] The exact meaning of these syndromes is, however, unclear, as is their relationship with post–treatment discontinuation recurrence risk. What we do not know is whether onset of withdrawal symptoms on discontinuation of antidepressant drugs may be related to an increased vulnerability to depressive relapse and/or resistance on reinstitution of drug treatment and/or loss of clinical effects during maintenance therapy. The issue has important clinical implications, since different antidepressant drugs may yield different rates of withdrawal syndromes.[79]

We know that discontinuation of antidepressant drugs may trigger hypomania or mania[81,82] despite adequate concomitant mood-stabilizing treatment.[83] Furthermore, mood shifts to euthymia or hypomania are not rare events in patients withdrawn from medication because of a lack of efficacy.[84] Mood elevation may also occur with antidepressant dose decrease,[85] and patients who failed to respond to mood stabilizers in combination with antidepressant drugs may improve on discontinuation of the antidepressant drugs.[86] These data suggest a relationship between antidepressant drug discontinuation and cycle acceleration in bipolar disorder.[83] In unipolar depression, withdrawal phenomena may be associated with recurrence acceleration.

PATHOPHYSIOLOGIC MECHANISMS

If we try to view under a unifying light the clinical phenomena that have been described, we must refer to the concept of tolerance. Decremental pharmacodynamic models of tolerance, which focus on processes that change the number or properties of drug-sensitive receptor populations, have very limited explanatory power in terms of the clinical phenomena previously described. The oppositional model of tolerance,[87] however, seems to entail several important implications. According to this model, continued drug treatment may recruit processes that oppose the initial acute effects of a drug or of receptor alterations. This model may explain the onset of tolerance in some patients. Use of antidepressant drugs may also propel the illness to a more malignant and treatment-unresponsive course, as was suggested in bipolar disorder.

When drug treatment ends, oppositional processes may operate for some time, resulting in appearance of withdrawal symptoms and increased vulnerability to relapse. As Baldessarini[20] remarks, the assumption that such physiologic processes will readjust after a withdrawal phase is not supported by current awareness in the field of drug dependence. Several months may be necessary (or the processes may even have an irreversible connotation), as has been found with, for instance, the sex-specific residual effects of cannabis on visuospatial memory.[88] What type of oppositional processes can be recruited and/or sensitized by antidepressant drugs is open to question. Several hypotheses may be formulated.

Interactions Between Different Types of Serotonin Receptors

There is increasing awareness of the complex mutual inhibitory effects of different serotonin receptors, particularly 5-HT_1 and 5-HT_2 receptors.[89] Berendsen[90] has suggested that an important function of antidepressants is to restore a disturbed balance between 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 receptors. It is, therefore, conceivable that a therapeutic action of antidepressant drugs (e.g., down-regulation of postsynaptic 5-HT_2 receptors) may, under certain conditions, trigger changes in postreceptor signal transduction, in intraneuronal signaling pathways, or in neuronal architecture that are likely to affect the balance of serotonin receptors. There is preclinical evidence of the autoregulation of serotonin and its potential effect on neurogenesis.[91,92] Jacobs et al.[93] have recently proposed an impairment in neurogenesis as the key pathophysiologic event in depression.

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Interactions Between Different Neurotransmitters

In the same vein, there is increasing awareness of the complex mutual inhibitory effects of different neurotransmitter systems that may be affected in depression.[89] Antidepressant drugs may yield changes in connections or sensitivity to neurotransmitters indirectly related to the specific actions.

Interactions Between Neurotransmitter Balance and the Hypothalamic-Pituitary-Adrenal Axis

Neurophysiologists have used the term *sensitization*, as opposed to *habituation*, to refer to the long-lasting increment in response occurring on repeated presentation of a stimulus that reliably elicits a response at its initial presentation.[94] Psychostimulants such as amphetamine and cocaine have been found to induce sensitization. Antidepressant therapy, however, may also induce time-dependent sensitization.[95]

There is extensive evidence that the hypothalamic-pituitary-adrenal (HPA) axis, through an action on corticotropin-releasing factor neurons,[96] can modulate both sensitization and tolerance.[97] Of particular interest is the relationship between serotonin receptors and HPA axis.[98] By facilitating 5-HT_1 receptor–mediated neurotransmission, 5-HT_2 postsynaptic down-regulation, a putative final common pathway of the actions of different antidepressants,[89] may induce an activation of the HPA axis. This activation, in turn, may unfavorably affect serotonin receptor functioning.[99] An example of this interaction is provided by the use of specific 5-HT_2 receptor antagonists (ritanserin and ketanserin) in Cushing's disease, which often yields only a temporary decrease in adrenocorticotropic hormone (ACTH) and cortisol secretion, followed by an escape phenomenon.[100]

An impressive body of evidence[101,102] supports the concept of an antidepressant mechanism of action that exerts its effects beyond the cell membrane receptors of biogenic amines and leads to enhanced glucocorticoid receptor function and expression. Thus, the phenomena observed with long-term use of serotonin receptor antagonists in Cushing's disease have considerable relevance, particularly considering the fact that long-term treatment with inhibitors of steroid production is unlikely to yield the same phenomenon.[98] It has thus been postulated[98] that long-term treatment with antidepressant drugs in nonendocrine depression, after an initial phase of normalization of the HPA axis, may recruit its ACTH-dependent activation, which results in loss of clinical effect. The poor prognosis of remitted patients who still display abnormalities of the HPA axis is in line with this hypothesis.[98]

Activation of hormonal markers of stress response following discontinuation of SSRI has been described[103] and thus may lead to increased vulnerability to relapse in susceptible individuals.

Cross-Sensitization With Behavioral and Cognitive Phenomena

Activation of the HPA axis may be permissive for repeated psychostimulant sensitization.[96] Indeed, the acute and sensitizing effects of amphetamine are diminished by adrenalectomy. There is considerable evidence of cross-sensitization between psychoactive drugs and environmental stressors,[104] and such cross-sensitization may be HPA mediated.

Post[105] postulated that both sensitization to stressors and episode sensitization may occur in mood disorders and became encoded at the level of gene expression. In particular, stressors and the biochemical concomitants of the episode can themselves induce the proto-oncogene c-*fos* and related transcription factors, which then affect the expression of transmitters, receptors, and neuropeptides that alter responsiveness in a long-lasting way.[105] Segal et al.[106] extended these possibilities to negative patterns of information processing, and Benazzi[107] extended them to residual symptomatology. In this context, antidepressant drugs may display a protective effect. We cannot exclude, however, that—through an action mediated by the HPA axis—they may also potentiate both sensitization of stressors and episode sensitization.

CAN THE SENSITIZATION HYPOTHESIS BE TESTED?

Verifying the occurrence of potential sensitizing effects of antidepressant drugs in depression entails considerable methodological difficulties. A basic problem is that the use of antidepressant drugs is so prevalent that it is difficult to recruit clinical populations who have never been exposed to them. Furthermore, any intervention design contemplated is likely to affect many crucial variables. For instance, there is increasing evidence[108] that CBT appears to reduce the risk of depressive relapse and may have a more durable effect than pharmacotherapy alone. However, the differences may be due to some protective effects of CBT more than to the occurrence of sensitizing effects from the use of antidepressant drugs. There is some evidence[109–113] suggesting that CBT may reduce residual symptomatology, which is probably the most powerful risk factor for relapse in unipolar depression.[12] Researchers thus should demonstrate that the combination of psychotherapy and pharmacotherapy is inferior in terms of relapse prevention to psychotherapy alone.

In a controlled trial study,[114] patients with recurrent depression were allocated to 3 groups: short-term and maintenance (2 years') treatment with antidepressant drugs, CBT in the short-term and maintenance phases, and antidepressant use in the short-term phase and CBT for maintenance. Cognitive therapy displayed a similar prophylactic effect to maintenance medication. The long-

term outcome of the group receiving both short-term and maintenance treatment with cognitive therapy was slightly better than that of the group who received pharmacotherapy followed by psychotherapy.[114] Furthermore, an additive effect of combination therapy has been shown only with the more complex depressive disorders.[115] However, all results may be affected by the presence of patients who were previously treated with antidepressant drugs. This is just an example of the difficulties that may be encountered in testing the hypothesis.

So far, only 1 study has specifically attempted to verify this sensitization hypothesis. Young et al.[116] investigated the response to desipramine treatment in relation to prior antidepressant treatment. Patients with past antidepressant treatment had more episodes of depression and a longer duration of illness; however, this may simply reflect the more severe course of their illness and not an antidepressant effect. Young et al.[116] failed to substantiate a relationship between prior antidepressant therapy and a lower response to further antidepressant therapy.

Despite considerable methodological difficulties, several research strategies may yield valuable information as to the sensitization hypothesis.

Controlled Clinical Trials

Controlled clinical trials may provide valuable information only if they are associated with an adequate follow-up period (at least 2 years). These trials achieve considerable validity if they compare drug treatment and placebo or clinical management in patients who have had no previous exposure to antidepressant drugs.

Three types of trials appear to be particularly suitable. One is studies of children and adolescents, since they are more likely to be experiencing their first episode of major depression and antidepressant drug treatment does not appear to be superior to placebo.[117] Another type of trial involves situations in which there were no significant differences between drug and placebo in the short term (e.g., in minor depression).[118] A third type of trial involves the use of antidepressant drugs in anxiety disorders (particularly panic, social phobia, and obsessive-compulsive disorder). It is conceivable that, once drug treatment has been discontinued, despite substantial clinical improvement in anxiety symptoms during active treatment, patients treated with antidepressant drugs may suffer from episodes of major depression more than patients treated with placebo or benzodiazepines.

Biological Studies

The use of biological markers has provided important insights into the psychobiology of depression. Unfortunately, however, most of the studies have been cross-sectional and did not include longitudinal follow-up of patients. Yet, very important clinical results have been achieved with this strategy. For instance, reversion to abnormal dexamethasone suppression test results after initial normalization on antidepressant drug treatment[119] may reflect either the progression of illness or a delayed sensitizing effect of antidepressant drugs on the HPA axis. Positron emission tomographic imaging of serotonin transporters may be another helpful modality for dissecting sensitizing effects.

CLINICAL IMPLICATIONS OF THE SENSITIZATION HYPOTHESIS

If the hypothesis that antidepressant drugs might unfavorably affect the outcome of depression in some or all depressed patients were substantiated by research evidence, a number of clinical issues would emerge. Treatment of depression by antidepressant drugs would not be questioned in itself, yet information about sensitization may yield a more informed use of pharmacotherapy.

Inappropriate Use of Antidepressant Drugs

The effectiveness of antidepressant drugs is firmly established in major depressive disorders.[6] However, there is a growing tendency to also use them in the setting of a collection of dysphoric complaints or demoralization.[8] This tendency has been considerably increased by the introduction of the SSRIs because of their better tolerability compared with that of the tricyclics.[120,121]

Carroll[122] warned about inappropriate use of antidepressant drugs almost 2 decades ago: "[W]e strongly suspect that many patients who are simply unhappy or dysphoric receive these drugs, with predictable consequences in terms of morbidity from side effects, mortality from overdose, economic waste, and irrational, unproductive clinical management."[(p169)] To the same extent that tardive dyskinesia has limited inappropriate use of antipsychotics and antibiotics should not be routinely prescribed for minor, viral ailments, an inappropriate use of antidepressant drugs may lead to a deterioration of clinical course with no clear benefit.

Dependence Versus Sensitization

The issue of dependence has shifted drug treatment of anxiety disorders from use of benzodiazepines to antidepressant drugs. Once again, let us assume that antidepressants may worsen the course of depression. Such treatment would increase vulnerability to depression. Paradoxically, benzodiazepines might be reevaluated, since dependence could be regarded as a lesser problem.

Full Versus Subtherapeutic Dosage of Antidepressants

There is increasing consensus about the advantage of maintaining patients at the acute treatment dosage.[60] The rationale for this choice would be the insufficient protective effects of subtherapeutic doses. Keeping a patient on treatment with low-dose antidepressants for a long time

(a very common practice, particularly by nonpsychiatric physicians, in Europe) would expose the patient to the risks of sensitization without an adequate protective effect.

Acute Versus Prophylactic Effect of Antidepressants

The full-dose continuation treatment strategies, however, endorse a hidden conceptual model: that what is effective acutely in depression is also the best option for continuation treatment. The stages of development of a disorder would not be influential in guiding the treatment. There is evidence, however, to call such views into question.[12]

Antidepressant drugs were developed for and found to be effective in the treatment of major depressive episodes.[6] In recent years, their use has been extended to maintenance and prevention.[31] However, treatments that are effective in the acute phase of illness are not necessarily the most suitable for postacute and residual phases or maintenance.[3] Different antidepressant drugs may yield a differential rate of tolerance in the long term, with particular reference to the HPA axis.[98]

Discontinuation of Antidepressant Drugs

Baldessarini[20] described the risks and implications of abruptly interrupting maintenance drug therapy and the clinical advantages of a gradual decrease. It is astonishing how little we know about practical issues such as discontinuation of antidepressant drugs. Similarly, there is insufficient biological exploration of antidepressant withdrawal.[103] However, the issue of withdrawal phenomena is getting increasing attention with the use of SSRIs.[75–80]

Are withdrawal phenomena simply bothersome and self-limiting reactions, or are they a manifestation of an increased vulnerability to relapse once drug treatment has been discontinued? There is evidence that certain SSRIs are more likely to induce withdrawal reactions than others.[78,79] According to the oppositional tolerance model, this would mean that they also facilitate (or fail to protect from) relapse once they are discontinued. This effect could explain the high rate of relapse on switching from an SSRI to placebo, which may be different from one drug to another and be demonstrated by follow-up studies.

Psychotherapeutic Versus Pharmacologic Changes

Biondi[123] emphasized how both acute stressors and psychotherapy can induce biological modifications at the central level and how psychotropic drugs and psychological interventions are probably acting on common neurotransmitter pathways. The extent and type of action, however, may be different and, from this, differential therapeutic efforts may ensue.

Substantial evidence supports the efficacy of long-term antidepressant medication in patients with recurrent depression.[31,124] However, recent research[112,114,125–127] indicates that cognitive-behavioral strategies may yield similar results in recurrent depression, whereas the role of cognitive-behavioral strategies in bipolar disorder is yet to be established.[128,129] If the sensitization hypothesis were correct, nonpharmacologic strategies for maintenance would achieve even greater importance.

CONCLUSION

At present, we have no sound data to support the view that antidepressant drugs may worsen the course of depression, and, if they do, whether the phenomenon is generalized or very limited. Randomized controlled trials are conducted with heterogeneous groups of patients, and the trial results represent an estimate of the average difference in the responses of the treatment groups. A treatment that is helpful on average may be harmful for some patients, as shown by a reanalysis of the Beta-Blocker Heart Attack Trial.[130] There is only a high degree of suspicion if we examine various clinical phenomena reported in the literature. We have no sound data, however, to exclude the possibility that antidepressant drugs worsen the course of depression.

The scientific study of oppositional tolerance in depression entails considerable methodological problems. Yet, many important data have probably been inadvertently collected in the progress of clinical studies on depression (e.g., on resistance) and on antidepressant drugs in the setting of anxiety disorders. Certainly, researchers working along these lines are likely to encounter tremendous difficulties in disclosing their results in journals and symposia or in getting their studies started and funded, in view of the current ideological and pharmaceutically driven[131–134] climate. They should be ready to bear with the retaliation that outliers receive in these situations. Yet, it is time to debate and explore these issues of crucial clinical value.

There are no feasible alternatives to treating major depressive episodes with antidepressant drugs, and potential adverse phenomena are overshadowed by this clinical consideration. However, appraisal of these side effects may yield important insights into the modalities of such practice and into preventing recurrences with long-term antidepressant drug therapy. At present, it is impossible to know whether antidepressant drugs fail to improve the long-term course of depression (despite shortening the episodes) or worsen its course. Yet, at present, the oppositional tolerance model applied to antidepressant drugs may provide room for a number of clinical phenomena that would otherwise lack explanation. We should be aware that we are stretching the original indications (major depressive episodes) of drugs of modest efficacy[135] to include prevention of relapse, anxiety disorders, and demoralization. Antidepressant drugs may speed improvement and change the boundary between "responders" and

"nonresponders." However, when we prolong treatment to more than 6 to 9 months, we may recruit different phenomena, such as tolerance, episode acceleration, and paradoxical effects.[136] Commonly shared clinical assumptions (the longer the antidepressant drug treatment, the better; the higher the dosage, the better) are challenged by research evidence. It is time to switch gears in depression research and start tackling the basic issues concerned with long-term treatment of depression.

Drug names: amitriptyline (Endep, Elavil, and others), clonazepam (Klonopin and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil, Surmontil, and others), nortriptyline (Aventyl and others), phenelzine (Nardil), sertraline (Zoloft).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES

1. Piccinelli M, Wilkinson G. Outcome of depression in psychiatric settings. Br J Psychiatry 1994;164:297–304
2. Paykel ES. Relapse, recurrence and chronicity in depression. In: Langer SZ, Brunello N, Racagni G, et al, eds. Critical Issues in the Treatment of Affective Disorders. Basel, Switzerland: Karger; 1994:9–20
3. Fava GA. The concept of recovery in affective disorders. Psychother Psychosom 1996;65:2–13
4. Andrews G. Should depression be managed as a chronic disease? BMJ 2001;322:419–421
5. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet 1997;139:1498–1504
6. Fava M, Kendler KS. Major depressive disorder. Neuron 2000;28: 335–341
7. Michoulon D, McColl Vuolo R, Howarth S, et al. Management of major depression in the primary care setting. Psychother Psychosom 2001;70:103–107
8. Fava GA, Mangelli L, Ruini C. Assessment of psychological distress in the setting of medical disease. Psychother Psychosom 2001;70:171–175
9. Schneider G, Kruse A, Nehen HG, et al. The prevalence and differential diagnosis of subclinical depressive syndromes in inpatients 60 years or older. Psychother Psychosom 2000;69:251–260
10. Ramana R, Paykel ES, Cooper Z, et al. Remission and relapse in major depression. Psychol Med 1995;25:1161–1170
11. Lin EHB, Simon GE, Katon WJ, et al. Can enhanced acute-phase treatment of depression improve long-term outcomes? Am J Psychiatry 1999;156:643–645
12. Fava GA. Subclinical symptoms in mood disorders. Psychol Med 1999;29:47–61
13. Quitkin FM, Stewart JW, McGrath PJ, et al. Loss of drug effects during continuation therapy. Am J Psychiatry 1993;150:562–565
14. El-Mallakh RS, Waltrip C, Peters C. Can long-term antidepressant use be depressogenic? [letter with reply] J Clin Psychiatry 1999;60:263
15. Fahn S. Levodopa-induced neurotoxicity: does it represent a problem for the treatment of Parkinson's disease? CNS Drugs 1997;8:376–393
16. Mitchell EA. Is current treatment increasing asthma mortality and morbidity? Thorax 1989;44:81–84
17. Sears MR. Long-acting beta-agonists, tachyphylaxis, and corticosteroids. Chest 1996;109:862–864
18. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. Annu Rev Public Health 1998;19:55–72
19. Fava GA. Do antidepressant and antianxiety drugs increase chronicity in affective disorders? Psychother Psychosom 1994;61:125–131
20. Baldessarini RJ. Risks and implications of interrupting maintenance psychotropic drug therapy. Psychother Psychosom 1995;63:137–141
21. Fava GA. Holding on: depression, sensitization by antidepressant drugs, and the prodigal experts. Psychother Psychosom 1995;64:57–61
22. Fava GA. Potential sensitizing effects of antidepressant drugs on depression. CNS Drugs 1999;12:247–256
23. Viguera AC, Baldessarini RJ, Friedberg J. Discontinuing antidepressant treatment in major depression. Harv Rev Psychiatry 1998;5:293–306
24. Baldessarini RJ, Ghaemi SN, Viguera AC. Tolerance in antidepressant treatment. Psychother Psychosom 2002;71:177–179
25. Schmidt ME, Fava M, Zhang S, et al. Treatment approaches to major depressive disorder relapse, part 1: dose increase. Psychother Psychosom 2002;71:190–194
26. Brugha TS, Bebbington PE, MacCarthy B, et al. Antidepressants may not assist recovery in practice. Acta Psychiatr Scand 1992;86:5–11
27. Dawson R, Lavori PW, Coryell WN, et al. Maintenance strategies for unipolar depression. J Affect Disord 1998;49:31–44
28. Reimherr FW, Amsterdam JD, Quitkin FM, et al. Optimal length of continuation therapy in depression. Am J Psychiatry 1998;155: 1247–1253
29. Stassen HH, Delini-Stula A, Angst J. Time course of improvement under antidepressant treatment: a survival-analytical approach. Eur Neuropsychopharmacol 1993;3:127–135
30. Baldwin RC. Antidepressants in geriatric depression: what difference have they made? Int Psychogeriatrics 1995;7(suppl):55–68
31. Kupfer DJ. Maintenance treatment in recurrent depression. Br J Psychiatry 1992;161:309–316
32. Di Mascio A, Meyer RE, Stifler L. Effects of imipramine on individuals varying in level of depression. Am J Psychiatry 1968;127(suppl):55–58
33. Van Scheyen JD. Recurrent vital depressions. Psychiatr Neurol Neurochir 1973;76:93–112
34. Healy D. Emergence of antidepressant induced suicidality. Prim Care Psychiatry 2000;6:23–28
35. Aronson TA. Treatment emergent depression with antidepressants in panic disorder. Compr Psychiatry 1989;30:267–271
36. Fux M, Taub M, Zohar J. Emergence of depressive symptoms during treatment for panic disorder with specific 5-hydroxytryptophan reuptake inhibitors. Acta Psychiatr Scand 1993;88:235–237
37. Barlow DH, Gorman JM, Shear KM, et al. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder. JAMA 2000;285:2529–2536
38. Brown TA, Barlow DH. Long-term outcome in cognitive behavioral treatment of panic disorder. J Consult Clin Psychol 1995;63:754–765
39. Otto MW, Pollack MH, Sabatino SA. Maintenance of remission following cognitive behavior therapy for panic disorder. Behav Therapy 1996;27:473–482
40. Fava GA, Rafanelli C, Grandi S, et al. Long-term outcome of panic disorder with agoraphobia treated by exposure. Psychol Med 2001;31:891–898
41. Noyes R, Garvey HJ, Cook BL. Follow-up study of patients with panic disorder and agoraphobia with panic attacks treated with tricyclic antidepressants. J Affect Disord 1989;16:249–257
42. Molnar G, Gupta RN. Plasma levels and tricyclic antidepressant therapy. Biopharm Drug Dispos 1980;1:283–305
43. Cain JW. Poor response to fluoxetine. J Clin Psychiatry 1992;53: 272–277
44. Fichtner CG, Jobe TH, Braun BG. Possible therapeutic window for serotonin reuptake inhibitors [letter with reply]. J Clin Psychiatry 1994;55:36–37
45. Pitchot W, Gonzales-Moreno A, Ansseau M. Therapeutic window for 5-HT reuptake inhibitors [letter]. Lancet 1992;339:684
46. Fichtner CG, Jobe TH, Braun BG. Does fluoxetine have a therapeutic window? [letter] Lancet 1991;338:520–521
47. Benazzi F. A therapeutic window with citalopram in a case of depression [letter]. Pharmacopsychiatry 1996;29:42
48. Post RM, Denicoff KD, Leverich GS, et al. Drug-induced switching in bipolar disorder. CNS Drugs 1997;8:352–365
49. Angst J. Switch from depression to mania: a record study of decades between 1920 and 1982. Psychopathology 1985;18:140–155
50. Kukopulos A, Reginaldi D, Laddomada P, et al. Course of the manic-depressive cycle and changes caused by treatments. Pharmakopsychiatr Neuropsychopharmakol 1980;13:156–167
51. Kukopulos A, Caliari B, Tundo A, et al. Rapid cyclers, temperament, and antidepressants. Compr Psychiatry 1983;24:249–258
52. Perini GI, Fava GA, Morphy MA, et al. The metyrapone test in affective disorders and schizophrenia: changes upon treatment. J Affect Disord

1984;7:265–272
53. Goodwin FK. The biology of recurrence: new directions for the pharmacologic bridge. J Clin Psychiatry 1989;50(12, suppl):40–44
54. Byrne SE, Rothschild AJ. Loss of antidepressant efficacy during maintenance therapy: possible mechanisms and treatments. J Clin Psychiatry 1998;59:279–288
55. Cohen BM, Baldessarini RJ. Tolerance to therapeutic effects of antidepressants. Am J Psychiatry 1985;142:489–490
56. Fava M, Rappe SM, Pava JA, et al. Relapse in patients on long-term fluoxetine treatment: response to increased fluoxetine dose. J Clin Psychiatry 1995;56:52–55
57. Mann JJ. Loss of antidepressant effect with long term monoamine oxidase inhibition. J Clin Psychopharmacol 1983;3:363–366
58. Lieb J, Balter A. Antidepressant tachyphylaxis. Med Hypotheses 1984;15:279–291
59. Franchini L, Rossini S, Bongiorno F, et al. Will a second prophylactic treatment with a higher dosage of the same antidepressant either prevent or delay new depressive episodes? Psychiatry Res 2000;96:81–85
60. Frank E, Kupfer DJ, Perel JM, et al. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990;47:1093–1099
61. Marks IM. Behavioral and drug treatments of phobic and obsessive-compulsive disorders. Psychother Psychosom 1986;46:35–44
62. Fava GA. Fading of therapeutic effects of alprazolam in agoraphobia. Prog Neuropsychopharmacol Biol Psychiatry 1988;12:109–112
63. Post RM, Leverich GS, Altshuler L, et al. Lithium discontinuation-induced refractoriness. Am J Psychiatry 1992;149:1727–1729
64. Maj M, Pirozzi R, Magliano L. Nonresponse to reinstituted lithium prophylaxis in previously responsive bipolar patients: prevalence and predictors. Am J Psychiatry 1995;152:1810–1811
65. Faedda GL, Tondo L, Baldessarini RJ, et al. Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. Arch Gen Psychiatry 1993;50:448–455
66. Coryell W, Solomon D, Leon AC, et al. Lithium discontinuation and subsequent effectiveness. Am J Psychiatry 1998;155:895–898
67. Fava GA, Rafanelli C, Grandi S, et al. Six-year outcome for cognitive behavioral treatment of residual symptoms in major depression. Am J Psychiatry 1998;155:1443–1445
68. Friedman RA, Mitchell J, Kocsis JH. Retreatment for relapse following desipramine discontinuation in dysthymia. Am J Psychiatry 1995;152:926–928
69. Donaldson SR. Tolerance to phenelzine and subsequent refractory depression: three cases. J Clin Psychiatry 1989;50:33–35
70. Fava M, Schmidt ME, Zhang S, et al. Treatment approaches to major depressive disorder relapse, part 2: re-initiation of antidepressant treatment. Psychother Psychosom 2002;71:195–199
71. Maina G, Albert U, Bogetto F. Relapses after discontinuation of drug associated with increased resistance to treatment in obsessive-compulsive disorder. Int Clin Psychopharmacol 2001;16:33–38
72. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996;19:179–200
73. Kramer JC, Klein DF, Fink M. Withdrawal symptoms following discontinuation of imipramine therapy. Am J Psychiatry 1961;118:549–550
74. Dilsaver SC. Heterocyclic antidepressant, monoamine oxidase inhibitor and neuroleptic withdrawal phenomena. Prog Neuropsychopharmacol Biol Psychiatry 1990;14:137–161
75. Lejoyeux M, Adès J, Mourad I, et al. Antidepressant withdrawal syndrome. CNS Drugs 1996;5:278–292
76. Zajecka J, Tracy KA, Mitchell S. Discontinuation symptoms after treatment with serotonin reuptake inhibitors: a literature review. J Clin Psychiatry 1997;58:291–297
77. Medawar C. The antidepressant web. Int J Risk Safety Med 1997;10: 75–126
78. Oliver JS, Burrows GD, Norman TR. Discontinuation syndromes with selective serotonin reuptake inhibitors. CNS Drugs 1999;12:171–177
79. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998;44:77–87
80. Fava GA, Grandi S. Withdrawal syndromes after paroxetine and sertraline discontinuation. J Clin Psychopharmacol 1995;15:374–375
81. Mirin SM, Schatzberg AF, Creasey DE. Hypomania and mania after withdrawal of tricyclic antidepressants. Am J Psychiatry 1981;138: 87–89
82. Landry P, Roy L. Withdrawal hypomania associated with paroxetine [letter]. J Clin Psychopharmacol 1997;17:60–61
83. Goldstein TR, Frye MA, Denicoff KD, et al. Antidepressant discontinuation-related mania: critical prospective observation and theoretical implications in bipolar disorder [CME]. J Clin Psychiatry 1999;60:563–567
84. McGrath PJ, Stewart JW, Tricamo E, et al. Paradoxical mood shifts to euthymia or hypomania upon withdrawal of antidepressant agents. J Clin Psychopharmacol 1993;13:224–225
85. Corral M, Sivertz K, Jones BD. Transient mood elevation associated with antidepressant drug decrease. Can J Psychiatry 1987;32:764–767
86. Sharma V. Loss of response to antidepressants and subsequent refractoriness. J Affect Disord 2001;64:99–106
87. Young AM, Goudie AJ. Adaptive processes regulating tolerance to behavioral effects of drugs. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology. New York, NY: Raven Press; 1995:733–742
88. Pope HG, Jacobs A, Mialet JP, et al. Evidence for a sex-specific residual effect of cannabis on visuo-spatial memory. Psychother Psychosom 1997;66:179–184
89. Leonard BE. Serotonin receptors and their function in sleep, anxiety disorders, and depression. Psychother Psychosom 1996;65:66–75
90. Berendsen HG. Interactions between 5-hydroxytryptamine receptor subtypes. Pharmacol Ther 1995;66:17–39
91. Baker MW, Croll RP. Modulation of in vivo neuronal sprouting by serotonin in the adult CNS of the snail. Cell Mol Neurobiol 1996;16: 561–576
92. Diefenbach TJ, Sloley BD, Goldberg JI. Neurite branch development of an identified serotonergic neuron from embryonic Helisomer: evidence for autoregulation by serotonin. Dev Biology 1995;167:282–293
93. Jacobs BC, Van Praag H, Gage PH. Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry 2000;5:262–264
94. Groves PM, Thompson RF. Habituation: a dual-process theory. Psychol Rev 1970;77:419–450
95. Antelman SM, Gershon S. Clinical application of time-dependent sensitization to antidepressant therapy. Prog Neuropsychopharmacol Biol Psychiatry 1998;22:65–78
96. Koob GF, Cador M. Psychomotor stimulant sensitization: the corticotropin-releasing factor-steroid connection. Behav Pharmacol 1993;4:351–354
97. Ritzmann RF, Colbern DL, Zimmermann EG, et al. Neurohypophyseal hormones in tolerance and physical dependence. Pharmacol Ther 1984;23:281–312
98. Sonino N, Fava GA. CNS drugs in Cushing's disease: pathophysiological and therapeutic implications for mood disorders. Progr Neuropsychopharmacol Biol Psychiatry 2002;26:1011–1018
99. Van Praag HM. Faulty cortisol/serotonin interplay. Psychiatry Res 1996;65:143–157
100. Sonino N, Fava GA, Fallo F, et al. Effect of the serotonin antagonists ritanserin and ketanserin in Cushing's disease. Pituitary 2000;3:55–59
101. Holsboer F, Barden N. Antidepressants and the hypothalamic-pituitary-adrenocortical regulation. End Rev 1996;17:187–205
102. Pariante C, Miller AH. Glucocorticoid receptors in major depression. Biol Psychiatry 2001;49:391–404
103. Michelson D, Amsterdam J, Apter J, et al. Hormonal markers of stress response following interruption of selective serotonin reuptake inhibitor treatment. Psychoneuroendocrinology 2000;25:169–177
104. Stewart J, Badiani A. Tolerance and sensitization to the behavioral effects of drugs. Behav Pharmacol 1993;4:289–312
105. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992;149:999–1010
106. Segal ZV, Williams JM, Teasdale JD, et al. A cognitive science perspective on kindling and episode sensitization in recurrent affective disorder. Psychol Med 1996;26:371–380
107. Benazzi F. Prevalence and clinical correlates of residual depressive symptoms in bipolar II disorder. Psychother Psychosom 2001;70: 232–238
108. Scott J. Cognitive therapy of affective disorders. J Affect Disord 1996; 37:1–11
109. Fava GA, Grandi S, Zielezny M, et al. Cognitive behavioral treatment of residual symptoms in primary major depressive disorder. Am J Psychiatry 1994;151:1295–1299
110. Fava GA, Grandi S, Zielezny M, et al. Four-year outcome for cognitive behavioral treatment of residual symptoms in major depression. Am J

Psychiatry 1996;153:945–947
111. Fava GA, Savron G, Grandi S, et al. Cognitive-behavioral management of drug-resistant major depressive disorder [CME]. J Clin Psychiatry 1997;58:278–282
112. Fava GA, Rafanelli C, Grandi S, et al. Prevention of recurrent depression with cognitive behavioral therapy. Arch Gen Psychiatry 1998;55:816–820
113. Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy. Arch Gen Psychiatry 1999;56: 829–835
114. Blackburn IM, Moore RG. Controlled acute and follow-up trial of cognitive therapy and pharmacotherapy in out-patients with recurrent depression. Br J Psychiatry 1997;171:328–334
115. Wexler BE, Nelson JC. The treatment of major depressive disorders. Int J Ment Health 1993;22:7–41
116. Young LT, Cooke RG, Levitt AJ, et al. Prior antidepressant treatment does not have an impact on response to desipramine treatment in major depression. Biol Psychiatry 1995;38:410–412
117. Hazel P, O'Connell D, Heathcote D, et al. Efficacy of tricyclic drugs in treating child and adolescent depression. BMJ 1995;310:897–901
118. Paykel ES, Hollyman JA, Freeling P, et al. Predictors of therapeutic benefit from amitriptyline in mild depression. J Affect Disord 1988;14:83–85
119. Fava GA, Sonino N. Hypothalamic-pituitary-adrenal axis disturbances in depression. IRCS Med Sci 1986;14:1058–1061
120. Rosholm JU, Gram LF, Isacsson G, et al. Changes in the patterns of antidepressant use upon the introduction of new antidepressants. Eur J Clin Pharmacol 1997;52:205–209
121. Olfson M, Marcus SC, Pincus HA, et al. Antidepressant prescribing practices of outpatient psychiatrists. Arch Gen Psychiatry 1998;55: 310–316
122. Carroll BJ. Neurobiologic dimensions of depression and mania. In: Angst J, ed. The Origins of Depression. Berlin, Germany: Springer-Verlag; 1983:163–186
123. Biondi M. Beyond the brain-mind dichotomy and toward a common organizing principle of pharmacological and psychological treatments. Psychother Psychosom 1995;64:1–5
124. Fava M, Kaji J. Continuation and maintenance treatments of major depressive disorders. Psychiatr Ann 1994;24:281–290
125. Jarrett RB, Kraft D, Schaffer M, et al. Reducing relapse in depressed outpatients with atypical features. Psychother Psychosom 2000;69: 232–239
126. Jarrett RB, Kraft D, Doyle J, et al. Preventing recurrent depression using cognitive therapy with and without a continuation phase. Arch Gen Psychiatry 2001;88:381–388
127. Teasdale JD, Segal ZV, Williams JMG, et al. Prevention of relapse/ recurrence in major depression by mindfulness-based cognitive therapy. J Consult Clin Psychol 2000;68:615–623
128. Scott J, Garland A, Moorhead S. A pilot study of cognitive therapy in bipolar disorders. Psychol Med 2001;31:459–467
129. Fava GA, Bartolucci G, Rafanelli C, et al. Cognitive-behavioral management of patients with bipolar disorder relapsed while on lithium prophylaxis. J Clin Psychiatry 2001;62:556–559
130. Horwitz RI, Singer BH, Makuch RW, et al. Can treatment that is helpful on average be harmful to some patients? J Clin Epidemiol 1996;49:395–400
131. Fava GA. Conflict of interest and special interest groups. Psychother Psychosom 2001;70:1–5
132. Krimsky S. Journal policies on conflict of interest. Psychother Psychosom 2001;70:115–117
133. Garfinkel PE. The changing culture related to the practice of psychiatry. Psychother Psychosom 2001;70:227–231
134. Starcevic V. Opportunistic "rediscovery" of mental disorders by pharmaceutical industry. Psychother Psychosom 2002;71:305–310
135. Otto MW, Nierenberg AA. Assay sensitivity, failed trials, and the conduct of science. Psychother Psychosom 2002;71:241–243
136. Fava GA. Long-term treatment with antidepressant drugs. Psychother Psychosom 2002;71:127–132

For the CME Posttest for this article, see pages 223–224.