



Preventing Recurrent Depression: Long-Term Treatment for Major Depressive Disorder

This ACADEMIC HIGHLIGHTS section of *The Primary Care Companion to The Journal of Clinical Psychiatry* presents the highlights of the closed roundtable meeting "Preventing Recurrent Depression: Long-Term Treatment for Major Depressive Disorder," which was held on July 9, 2006, during the *Collegium Internationale Neuropsychopharmacologicum (CINP)* meeting in Chicago, Ill. This report was prepared by the University of California, Irvine School of Medicine, and the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Wyeth Pharmaceuticals.

The roundtable meeting was chaired by **David L. Dunner, M.D.**, from the Center for Anxiety and Depression, Mercer Island, Wash., and the Department of Psychiatry and Behavioral Sciences (professor emeritus), University of Washington, Seattle. The faculty were **Pierre Blier, M.D., Ph.D.**, from the Department of Psychiatry and the Department of Cellular Molecular Medicine, Institute of Mental Health Research, University of Ottawa, and the Mood Disorders Research Program, Royal Ottawa Hospital, Ontario, Canada; **Martin B. Keller, M.D.**, from the Department of Psychiatry and Human Behavior, Brown University School of Medicine, and Butler Hospital, Providence, R.I.; **Mark H. Pollack, M.D.**, from the Department of Psychiatry, Harvard Medical School, and the Center for Anxiety and Traumatic Stress Disorders, Massachusetts General Hospital, Boston; **Michael E. Thase, M.D.**, from the University of Pittsburgh School of Medicine and the Western Psychiatric Institute and Clinic, Pittsburgh, Pa., and the University of Pennsylvania School of Medicine, Philadelphia, Pa.; and **John M. Zajecka, M.D.**, from the Depression Treatment Research Center, Rush University Medical Center, Chicago, Ill.

Faculty disclosures appear at the end of the article.

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Major depressive disorder (MDD) is potentially a long-term or even lifelong illness for many patients, and maintenance therapy is designed to prevent relapse in patients with recurrent depression who have achieved remission. Patients who have residual symptoms, ongoing psychosocial stressors, or comorbid illnesses are among the suitable candidates for maintenance treatment. In the following discussion, experts in the treatment of depression address topics relevant to maintenance treatment: length of treatment, pharmacotherapy dosage, psychotherapy, and electroconvulsive therapy (ECT). Suggestions are also offered for improving subthreshold depressive symptoms and treatment adherence.

Dr. Dunner: We are going to discuss some issues that arise when treating MDD over the long term and attempting to prevent recurrent depression. Let us begin by talking about the difference between continuation therapy and maintenance therapy.

Continuation Therapy and Maintenance Therapy Differences

Dr. Keller: Continuation therapy is intended to prevent relapse, that is, to suppress the symptoms of a current depressive episode from which the patient has not fully recovered (Figure 1).¹ Usually, continuation therapy lasts 4 to 6 months after a patient has responded in the acute phase of treatment.²

Dr. Dunner: Yes, in continuation therapy studies, typical study design is to include patients who responded to an antidepressant during the acute

phase and then to continue some patients on antidepressant therapy and switch others to placebo. Antidepressant continuation therapy is in variably more effective than placebo, illustrating the need for continuation therapy with all treatments, including psychotherapy. For example, a review by Keller and Boland³ stated that the risk of relapse is greatest during the first 6 months after recovery and found that continuation therapy with antidepressant medications was effective (Table 1).³⁻⁸

Dr. Keller: In contrast to continuation therapy, *maintenance therapy* is a treatment designed to prevent recurrence, or the development of a new episode, once an acute episode and the continuation treatment phase are over (see Figure 1).¹ According to guidelines established by Hirschfeld,⁹ the duration of maintenance therapy is 6 to 24 months.

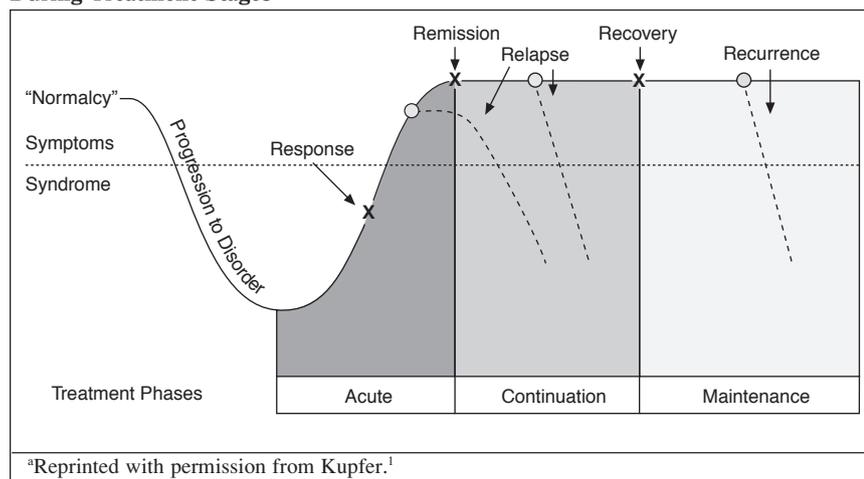
Dr. Thase: If other, more curative treatment options are not available, maintenance therapy may be needed for an indefinite amount of time for certain patients; maintenance therapy may translate into lifelong treatment.

Clinical Characteristics for Maintenance Therapy Candidacy for Major Depression

Dr. Dunner: Which patients should receive maintenance treatment for major depression, and which should not?

Dr. Thase: The key characteristics that qualify a patient with major depression for maintenance therapy are the number of prior episodes the patient has had and the frequency of recurrence. Patients who have had 2

Figure 1. Response, Remission, Recovery, Relapse, and Recurrence of Depression During Treatment Stages^a



^aReprinted with permission from Kupfer.¹

Table 1. Continuation Studies of Relapse Rates of Antidepressants Versus Placebo^a

Study	Drug	Relapse Rate	
		Drug (%)	Placebo (%)
Montgomery et al ⁴	Fluoxetine	26	57
Montgomery and Dunbar ⁵	Paroxetine	16	43
Doogan and Caillard ⁶	Sertraline	13	46
Montgomery et al ⁷	Citalopram	11	31
Feiger et al ⁸	Nefazodone	17	33

^aAdapted with permission from Keller and Boland.³

episodes within several years or a lifetime history of 3 or more episodes would be likely to show the greatest benefit from longer-term, preventive therapy.

Dr. Keller: I would consider anyone who has had 2 lifetime episodes in addition to the current episode to be a candidate; however, we need to also use good judgment when determining patients' eligibility for maintenance therapy and consider remission and risk factors for recurrence.

Dr. Zajecka: Only patients who have achieved remission and a score of less than 7 on the Hamilton Rating Scale for Depression (HAM-D)¹⁰ or 10 on the Montgomery-Asberg Depression Rating Scale (MADRS)¹¹ should be considered for maintenance treatment. Additionally, some other clinical characteristics—for example, residual symptoms or pregnancy—should be taken into account when supporting maintenance therapy candidacy.

Dr. Pollack: Ongoing psychosocial stressors and comorbidities should be considered too.

Dr. Dunner: Seasonal affective disorder (SAD) should also be considered.

Dr. Keller: Patients who have attained remission but are not asymptomatic—that is, 1 or 2 symptoms still persist—are at high risk for relapse and should continue to receive maintenance treatment.^{12,13} These persistent symptoms, or residual symptoms, in major depression may include difficulties in concentrating, sleep disturbances, subtle decreases in energy level, and minor persistent anxiety symptoms.

Dr. Thase: Patients who have residual depressive symptoms also tend to have a more severe course of illness, a greater burden of psychiatric and medical comorbidity, higher relapse rates, higher risk of suicide attempt, and poorer social functioning than

those patients who are asymptomatic.^{14–16}

Dr. Blier: A 12-year study by Judd and colleagues¹⁷ showed that patients with residual subthreshold symptoms, when compared with asymptomatic patients, had a more severe course of illness, had more chronic depressive episodes, and had a relapse or recurrence of the next major depressive episode more than 3 times faster.

Dr. Thase: Thus, proper assessment of patients' residual symptoms is essential to treat depression during the maintenance phase of therapy to optimize patient outcome.

Dr. Dunner: Evidence-based assessments such as the Beck Depression Inventory (BDI),¹⁸ the Patient Health Questionnaire (PHQ-9),¹⁹ and the Quick Inventory of Depressive Symptomatology (QIDS)²⁰ help clinicians accurately determine patients' symptom severity. When physicians use oral evaluations without rating scales, patients have a tendency to tell the physician that they "feel fine."

Dr. Pollack: Should treatment be continued in patients who meet the criteria for remission but who are involved in chaotic or stressful life situations or life events?

Dr. Dunner: Ongoing psychosocial stressors may negatively affect patients' daily functioning. Simons and colleagues²¹ found that the perceived impact of life stressors may initiate or prolong depressive episodes for patients who have been diagnosed with depression.

Dr. Keller: The Camberwell Collaborative Depression Study²² examined stressful variables for people who are in a first or second depressive episode. The results indicated that individuals who have low income are at higher risk for relapse, as are those in an acrimonious relationship.

Dr. Zajecka: Comorbid medical illnesses are also ongoing stressors. Patients who have illnesses such as cardiovascular disease, cancer, and diabetes that put them at greater risk

than people without comorbid medical illnesses for depression are also at high risk for relapse and should be considered for maintenance therapy.²³

Dr. Pollack: Anxiety commonly presents with depression, and monotherapy may not be effective in treating both disorders in maintenance therapy. Instead, medication augmentation, such as adding benzodiazepines to antidepressant treatment, may prevent or decrease the risk of relapse in this population.²⁴

Dr. Keller: Patients who are in their second episode and have poor symptom control or concomitant substance abuse are candidates for maintenance treatment as well.

Dr. Dunner: Seasonal affective disorder is a recurrent depression, and people with SAD are candidates for maintenance therapy instead of annual treatment.

Dr. Thase: Approximately 15% to 25% of people with recurrent depression have a fall-winter pattern of episodes,²⁵ making this a relatively prevalent type of depression. Phototherapy and other chronobiological interventions may have added value for treating patients with this disorder.^{26,27} Light boxes can be purchased at fairly reasonable prices relative to medication cost. I favor phototherapy to treat patients with mild symptomatology and pharmacotherapy to treat patients with more severe presentations of the illness.

Dr. Dunner: To prevent relapse or suicidal tendencies among patients with more severe SAD, I prefer to provide maintenance pharmacotherapy rather than to rely on patients to report annually for phototherapy treatment. Concerning pharmacotherapy, bupropion has been shown to be efficacious and is approved to treat SAD²⁸; however, studies of other medications have varying results.²⁹⁻³³

Dr. Zajecka: The point of treating this type of recurrent depression is to keep the patient in remission throughout the entire year, which may require the use of phototherapy, pharmaco-

therapy, or augmentation, depending on the individual patient.

Dr. Thase: Physicians should also provide ongoing supportive monitoring to their patients to minimize the risk of full-blown relapses.

Dr. Zajecka: Perhaps it is easier to identify patients who should *not* receive maintenance therapy. An example of a patient who can discontinue treatment is someone who has remitted from his or her first depressive episode, which was precipitated by a clear stressor, and who has no family history of depression. Another example is a young woman who has had 1 depressive episode, plans on having children, and does not want to take medication. Although any patient may be at risk for relapse, I recommend discontinuing treatment in these particular cases, keeping these patients under observation, and being prepared to treat them again if relapse occurs.

Dr. Dunner: The example of the young woman planning to have children raises an interesting question about the teratogenic risks of long-term pharmacotherapeutic treatments for major depression.

Dr. Thase: The risk of a recurrence of the mother's depression both during and following pregnancy is substantial, while the risk of teratogenicity for the fetus is uncertain. For example, Cohen and colleagues³⁴ showed a 68% relapse rate among antidepressant-treated women who were euthymic at conception and discontinued antidepressant medication during pregnancy, with a majority relapsing in the first trimester. There was also a 50% risk of postpartum depression.³⁴ Therefore, in the absence of alternative therapies, maintaining antidepressant medication will clearly result in better outcomes for the mother as opposed to discontinuing pharmacotherapy.

Dr. Blier: I'd like to stress that pregnancy does not protect against depression. Maintenance antidepressant therapy is necessary to prevent relapse, which may negatively impact both the mother and the fetus.

Dr. Dunner: There is a lack of data for the use of antidepressants during pregnancy. Generally, no syndrome is associated with the use of these agents. However, one study³⁵ found a significant association (odds ratio = 2.9; 95% confidence interval, 1.3 to 6.5) between persistent pulmonary hypertension in infants and exposure to selective serotonin reuptake inhibitors (SSRIs) after the 20th week of gestation.

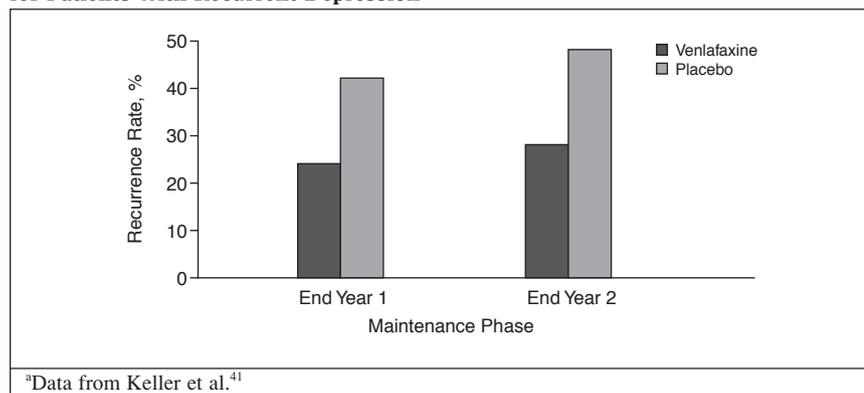
Dr. Blier: In a peer-reviewed editorial,³⁶ I discussed the study by Chambers and colleagues³⁵ that Dr. Dunner just mentioned, and I explained that when the entire pregnancy was examined, no significant association was reported, illustrating the lack of evidence for SSRIs as posing a teratogenic risk for pulmonary hypertension. Further, evidence^{37,38} that paroxetine causes cardiac malformations in infants has varied.

Dr. Keller: No adverse effects to the fetus have been found with fluoxetine, indicating that this medication may be safe to treat women during pregnancy.³⁹

Dr. Thase: In general, the mother's well-being is better if she continues on antidepressant treatment during pregnancy, but both the mother and father should be informed of any potential risk to the unborn child.

Maintenance Pharmacotherapy

Dr. Dunner: Let us discuss the data relating to the efficacy of maintenance pharmacotherapy for recurrent depression. A review by Hirschfeld⁴⁰ found that approximately 60% of patients at risk for recurrent depression, if left untreated, will have a depressive episode recurrence within 1 year; however, if patients maintain antidepressant treatment, between 10% and 30% will experience a recurrence, suggesting prophylactic efficacy of antidepressants in the treatment of recurrent depression.

Figure 2. Comparison of Relapse Rates for Maintenance Venlafaxine Versus Placebo for Patients With Recurrent Depression^a

Dr. Keller: My colleagues and I completed a progression of studies⁴¹ comprising a 10-week acute and a 6-month continuation phase of treatment, leading up to a 2-year maintenance phase of pharmacotherapy in patients with recurrent depression. The acute phase of treatment included 1096 patients who had at least 2 depressive episodes in addition to the current one within the past 5 years; those patients who responded to venlafaxine or fluoxetine and remained well progressed to the continuation phase of treatment. Patients who maintained a medication response over the 6-month period of treatment were then randomly assigned in a double-blind fashion to receive venlafaxine or placebo for the maintenance phase of treatment. During the first and second years of the maintenance phase,⁴¹ patients taking venlafaxine had lower rates of recurrent depression as compared with patients taking placebo (Figure 2).

Dr. Thase: In that progression of studies, doses up to 300 mg/day of venlafaxine were permitted, which is higher than the approved dose for the once-daily formulation; however, a secondary analysis of patients who received approved doses, i.e., 75 mg/day to 225 mg/day, confirmed the preventive effect of venlafaxine.

Dr. Keller: Many of us have patients with recurrent depression who, after almost 3 years of treatment, want to discontinue antidepressant medica-

tion; however, as the progression of studies⁴¹ we have been discussing showed, the risk for relapse seemed to increase over time rather than decrease. This increased risk for relapse was also illustrated in Frank and colleagues' study⁴² that examined imipramine versus placebo treatment in patients who had 2 prior depressive episodes in addition to the current episode over the past 5 years. After 3 years, fewer symptoms recurred in imipramine-treated patients than in patients who switched to placebo (20% and 80%, respectively).

Dr. Dunner: Further evidence of the benefit of long-term maintenance therapy is shown in a 2-year extension⁴³ of Frank and colleagues' 3-year study⁴²; in the 2-year extension, patients randomly assigned to placebo had substantially higher recurrence rates than those who remained on imipramine. Additionally, maintenance studies of citalopram⁴⁴ and sertraline⁴⁵ found that patients who remained on medication treatment had a longer time to depressive episode recurrence and fewer recurrences than those who were randomly assigned to placebo.

Dr. Pollack: Data⁴⁶ on panic disorder suggest that many patients who stop their medication may relapse or have recurrent symptoms but will respond when the treatment is restarted, although the response will be slower than during initial treatment. Regarding major depression, what is the

prospect of response to medication readministration once patients have initially responded to a particular drug and then subsequently discontinued that medication?

Dr. Zajecka: Patients who have achieved full remission may respond better to medication reinitiation than those patients who only had a partial response to the medication before stopping it. Fava and colleagues⁴⁷ found that, of patients who relapsed on placebo and were reinitiated into fluoxetine therapy, 62% responded.

Dr. Thase: In a study⁴⁸ of re-treatment conducted by my colleagues at the University of Pittsburgh, the time to response the second time was identical to the time to response the first time. Further, the duration of subsequent depressive episodes was greatly reduced because of early detection.

Dr. Blier: Early detection is important, because remission could be more difficult to attain if the patient is allowed to continue in the relapsed state.

Dr. Dunner: Is atypical depression different from other forms of depression with regard to the need for maintenance therapy?

Dr. Thase: Stewart and colleagues⁴⁹ studied patients diagnosed with atypical depression who achieved remission for at least 6 months with either phenelzine or imipramine and who then continued pharmacotherapy or were switched to placebo for another 6 months. Phenelzine, a monoamine oxidase inhibitor (MAOI), showed a clear protective effect during the subsequent 6-month maintenance phase while imipramine, a tricyclic antidepressant (TCA), did not. Patients who continued to take imipramine were nearly as likely to relapse as those who took placebo after imipramine therapy, whereas patients who continued taking phenelzine were 3 to 4 times less likely to relapse than those who had taken phenelzine and then placebo. Therefore, patients with atypical depression who respond to MAOI therapy are likely to get the same benefit from maintenance therapy as pa-

tients with other forms of recurrent depression, even though having reverse vegetative symptoms may increase patients' likelihood of responding to one type of treatment (MAOIs) over another (TCAs).

Duration and Dose of Maintenance Pharmacotherapy

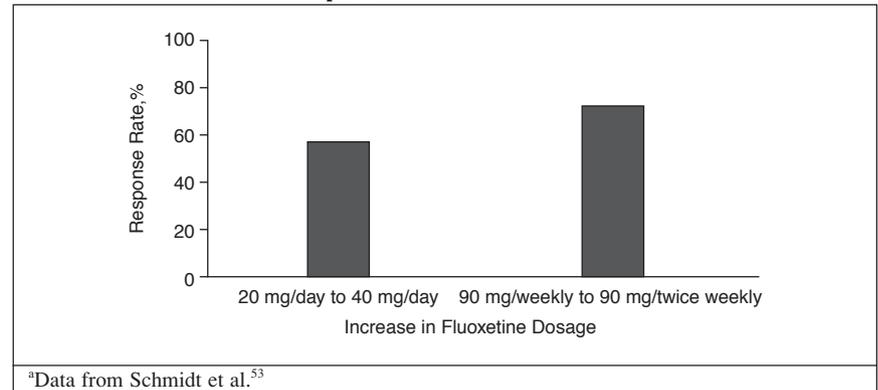
Dr. Dunner: In my understanding, the average duration of antidepressant treatment in the United States remains below that recommended by the Agency for Health Care Policy and Research Practice Guidelines (AHCPR),^{50,51} even though these guidelines were developed almost a decade ago.⁵² According to the AHCPR Practice Guidelines⁵⁰ for the treatment of major depression, acute episodes of depression should be treated for almost a year and recurrent episodes should be treated somewhat longer. Physicians, as a group, are not closely adhering to the established treatment guidelines when using pharmacotherapy to treat depression.

Dr. Zajecka: Clinicians should perceive depression as potentially being a lifelong illness that may require treatment indefinitely in many patients rather than as an illness that can usually be cured with a single, short course of treatment like an antibiotic.

Dr. Dunner: Should a female college student aged 20 who has recurrent depressive episodes take an antidepressant forever?

Dr. Thase: There is a difference between "forever" and "indefinitely." In the future, treatments that target the altered pathologic mechanisms of recurrent depression may be available and may have a more curative effect than the present medications, which suppress illness activity. Compared with currently available pharmacotherapeutic options, it may be possible to stop future treatments with fewer hazards. In the meantime, I recom-

Figure 3. Response Rates to an Increase in Fluoxetine Dosage Following Relapse in Patients With Recurrent Depression^a



mend that patients be advised to take treatment one year at a time.

Dr. Dunner: Let us discuss dosage recommendations for the maintenance phase.

Dr. Keller: Current evidence³ suggests that patients should be maintained on the same dose of medication that was necessary to achieve recovery or remission in the acute episode. Because of the absence of a large study using first-line treatments that provides evidence of equal efficacy after lowering the dosage of medication, I recommend maintaining the original pharmacotherapeutic dose to promote optimal patient outcome.

Dr. Dunner: The dose that got you better keeps you better.

Dr. Dunner: A study⁵³ examined increases in medication dosages for

patients who relapsed. In this study, patients with depression who responded to fluoxetine continued treatment for 25 weeks with 20 mg/day of fluoxetine or were switched to 90 mg/week of fluoxetine or to placebo. Those who relapsed during this phase of treatment had their doses of fluoxetine increased in the following manner: patients taking placebo were given 20 mg/day of fluoxetine, patients taking 20 mg/day were given 40 mg/day, and patients taking 90 mg/week received 90 mg/twice a week. A majority of those whose dose was increased responded (Figure 3).

Dr. Blier: As pharmacotherapy is prolonged, increases rather than decreases in drug dosage may be necessary to elicit favorable outcomes for patients.

Maintenance Psychotherapy

Dr. Dunner: What are the data for maintenance psychotherapy?

Dr. Keller: We have been talking about pharmacotherapy, but I want to emphasize that the proper treatment of patients with recurrent depression includes the combination of pharmacotherapy and at least one of the structured psychotherapies—mainly cognitive-behavioral therapy (CBT) or cognitive-behavioral analysis system of psychotherapy (CBASP); to use medication alone is insufficient treatment.¹³

Dr. Zajecka: In the early phases of treatment, CBT may prevent relapse, even in patients who discontinue their medication.^{54,55}

Dr. Keller: Compelling evidence for the value of psychotherapy is provided by a 3-phase study—acute, continuation, and maintenance treatment phases^{56–58}—that used a modified form of CBT called CBASP. In the 12-week acute phase of treatment,⁵⁶ patients randomly assigned to CBASP plus pharmacotherapy had a greater improve-

ment in psychosocial functioning and higher remission rates than patients who received pharmacotherapy or psychotherapy alone. In the 16-week continuation phase of treatment,⁵⁷ a greater number of patients maintained partial or full remission on the combination treatment (90%) as compared with the pharmacotherapy (80%) or psychotherapy alone (82%). In the 1-year maintenance phase of treatment,⁵⁸ patients in the CBASP group had significantly fewer recurrences ($p \leq .03$) than those patients in the assessment-only group. Patients who receive psychotherapy in the acute and continuation phases of treatment and achieve remission may be at a lower risk for recurrence during the maintenance phase of treatment than those patients who do not receive psychotherapy.

Dr. Pollack: Is there any evidence that CBT helps prevent relapse after discontinuation of medication?

Dr. Thase: Yes. Fava and colleagues conducted studies^{59,60} of maintenance CBT following pharmacotherapy discontinuation and found that patients who received CBT had lower levels of residual symptoms⁵⁹ or lower relapse rates⁶⁰ compared with those who did not receive CBT. These findings suggest that maintenance CBT offers a valid, nonpharmacotherapeutic alternative to the long-term use of antidepressants.

Dr. Pollack: Have there been studies that have added psychosocial treatments—whether CBT or other types—specifically around the time when antidepressants are being tapered to see if that would decrease the risk of relapse, as has been demonstrated with psychotherapy and benzodiazepines in panic disorder?⁶¹

Dr. Thase: Fava and colleagues^{62,63} developed a type of psychosocial therapy called personal well-being therapy, which was shown⁶³ to reduce residual symptoms, decrease the risk of relapse, and facilitate the subsequent withdrawal of antidepressant medications. Another study⁶⁴ used an emotion-focused modified form of CBT to

similarly reduce patients' risk for relapse. Both personal well-being therapy and emotion-focused therapy are promising strategies that have not yet been replicated by a multicenter group of collaborators.

An implicit assumption exists that all psychotherapies are the same. However, in a maintenance study,⁶⁵ the amount of time that the psychotherapist spent performing interpersonal psychotherapy (IPT) with patients was directly associated with whether IPT was efficacious for relapse prevention. When the psychotherapy had degenerated into supportive conversation—away from interpersonal theme areas—the value of IPT was identical to that of placebo. When the IPT remained focused on key psychotherapy themes, the psychotherapy efficacy approached that of imipramine. Thus, IPT was either a useful preventive treatment or an ineffective treatment, based on the quality and focus of the therapy.

Dr. Keller: Finding qualified psychotherapists is one of the keys to successful outcomes.

Dr. Pollack: Although we all recognize the efficacy of quality psychotherapy, the accessibility of these interventions may vary outside specialized treatment centers.

Dr. Keller: Finding psychotherapists who specialize in CBT or other modified forms of psychotherapy can be difficult, but the ideal treatment still is implementing these interventions into patients' treatment regimens. Primary care physicians are the main treaters of depression, and it is crucial

for these doctors to align themselves with a competent therapist to whom they can refer patients.

Dr. Thase: Primary care physicians should look for a therapist who responsibly handles referrals, gives feedback about patient well-being, seems to get at least half of the patients better, and receives good ratings from patients.

Dr. Pollack: Does anyone have any suggestions to help physicians find suitable therapists?

Dr. Dunner: I would like to recommend the Web site academyofct.org, through which cognitive-behavioral psychotherapists trained by Aaron Beck may be located.

Dr. Thase: Interpersonal psychotherapy may be easier to learn than Beck's full cognitive therapy, so nurse clinical specialists and others who provide that type of therapy may be more readily available.

Dr. Blier: The cost of psychotherapy can be a problem for patients. For example, a 1-hour session of CBT can amount to the cost of a 1-month prescription for an antidepressant, which can deter some patients from participating in this treatment option.

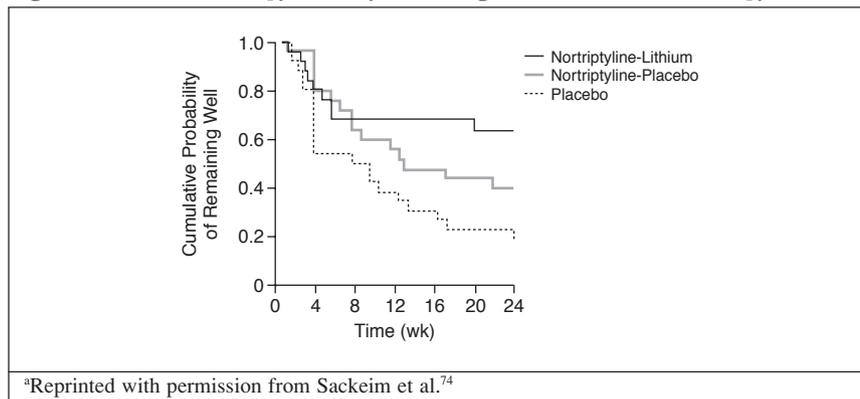
Dr. Thase: If cost or location presents a problem, Internet-based or telephone-based cognitive-behavioral psychotherapies are possible alternatives, and they have been shown to be efficacious for some patients.⁶⁶⁻⁷¹ However, online interventions should not be used to replace psychotherapy administered by an actual person, if that is an available option.

Maintenance Electroconvulsive Therapy

Dr. Dunner: What are the data regarding maintenance ECT?

Dr. Thase: Maintenance ECT should be used only as a last resort, that is, after patients have failed to respond to pharmacotherapy and psychotherapy.⁷² Although ECT can be dramatic, effective, and life-saving, it is

costly and life disrupting, so its place as a third- or fourth-line treatment for most forms of depression is well justified. However, where there is no alternative to help patients avoid an episode of depression, maintenance ECT can be used. Maintenance ECT may also be useful for treatment-resistant

Figure 4. Pharmacotherapy Efficacy Following Electroconvulsive Therapy^a

patients for whom vagal nerve stimulation (VNS) is appropriate treatment while they are waiting for the effects of VNS to ensue.

Dr. Zajecka: In a small study,⁷³ patients who previously failed pharmacotherapy and responded to acute ECT were then randomly assigned to receive either placebo or imipramine. Those patients who received imipramine had a much lower rate of relapse (18%)

than patients who received placebo (80%), indicating that patients might not have to receive ECT as a maintenance therapy after remission, even if ECT helped the depression remit.

Dr. Dunner: According to a study by Sackeim et al,⁷⁴ the combination of nortriptyline and lithium following ECT treatment was superior to placebo or medication monotherapy in preventing relapse (Figure 4).

Additional Considerations for Maintenance Therapy

Dr. Blier: One factor that is often overlooked in maintenance treatment trials is the issue of substance or alcohol use or abuse. In general, patients with dual diagnosis are not admitted into treatment trials because this comorbidity can decrease the remission rate.⁷⁵ Substance abuse can be a contributing factor for relapse, yet this comorbidity is often neglected when treating patients with recurrent depression.

Dr. Zajecka: Clinicians need to remain cognizant of the high comorbidity between affective disorders and substance use disorders.

Dr. Dunner: We need to discuss the topic of tachyphylaxis, or what has been called drug tolerance or the “poop-out” phenomenon, and consider how to deal with this confounding situation of apparent decreased medication effectiveness over time.

Dr. Zajecka: When the SSRIs came onto the market, some patients achieved a good response or full remission but, after some time, were described as apathetic and amotivated with a decreased range of affective response. Some people explained this experience by saying the medication stopped working. However, this phenomenon may be due to the fact that if medicines too selectively increase serotonin activity in the brain, there may be a compensatory decrease of norepinephrine and dopamine. To prevent this, physicians can start patients on a serotonin-norepinephrine reuptake inhibitor (SNRI).⁷⁶ Also, patients may respond to adjunctive noradrenergic or dopaminergic agents in addition to an SSRI.

Dr. Blier: I agree. After sustained administration of an SSRI, the atonic

activity of the norepinephrine neurons in the locus ceruleus decreases quite markedly—ranging from 30% to 70%, depending on the drug.⁷⁷ My colleagues and I have recently completed studies (B. Guiard, Ph.D.; M. El-Mansari, Ph.D.; P. Blier, M.D., Ph.D., unpublished data, 2006) showing that the serotonin neurons exert an inhibitory action on dopaminergic neurons in the ventral tegmental area. Therefore, the way Dr. Zajecka proposed managing tachyphylaxis is consistent with the neurobiological data.⁷⁷

Dr. Dunner: Tachyphylaxis is a presentation of anhedonia, a lack of motivation, and loss of libido. Tachyphylaxis should be distinguished from a true recurrence, which is a full return of symptoms, versus this emotional blunting phenomenon that may occur in patients who are euthymic. The term *tachyphylaxis* is sometimes used to describe both conditions and, therefore, may be used too broadly and inappropriately. Recurrence occurs with treatments other than SSRIs, such as TCAs⁴²; studies have found that about 1 in 4 patients who receive maintenance treatment for major depression experience a recurrence.⁷⁸ Determining if a patient has tachyphylaxis, recurrence, or a drug side effect is part of the differential diagnosis of patients who experience these symptoms while taking an antidepressant.

Dr. Thase: Another explanation for tachyphylaxis is that the patient’s improvement has been attributed to the active medication when in reality the patient remitted spontaneously or responded to the placebo effect. Perhaps the phenomenon is sometimes due to patients not being as adherent to their medication regimen as they say that they are.

Dr. Keller: What guidance can we give clinicians in encouraging their patients to remain adherent to medication?

Dr. Blier: Nonadherence is an important consideration in maintenance therapy. Approximately 50% of patients stop their medication prema-

Table 2. Reasons Patients May Become Nonadherent During Maintenance Pharmacotherapy

<p>Patients believe they will remain well</p> <p>Medication does not produce the desired outcome</p> <p>Serious adverse events or side effects occur</p> <p>Persistent sexual dysfunction</p> <p>Weight gain and other metabolic risk factors</p> <p>Presence of comorbid substance abuse</p>

turely and do not take it beyond 3 months.⁷⁹⁻⁸¹ Physicians should work to enhance patients' comfort level to ensure they adhere to treatment recommendations.

Dr. Dunner: Why do patients become nonadherent during this phase of treatment? (Table 2).

Dr. Keller: The obvious factors are that patients believe that they will remain euthymic after going off medication, or that the medication does not produce the desired outcomes, or that serious adverse events or side effects occurred while taking the medication.

Dr. Thase: Persistent sexual dysfunction, particularly when the patient was not aware that the medication could cause this adverse event, may be a strong motivator in stopping maintenance pharmacotherapy.⁸² Many patients in whom sexual dysfunction occurs are reluctant to discuss such a private issue with their physician and instead simply stop taking their medication.

Dr. Zajecka: Comorbid substance abuse may be a contributing factor to medication discontinuation, as well.

Dr. Dunner: Weight gain is another factor for medication discontinuation.⁸²

Dr. Thase: Weight gain is often a gradual process. Many antidepressants are weight neutral or even cause initial weight loss, but by the time patients reach the maintenance phase of treatment, some notice a substantial weight gain.

Dr. Blier: I recommend implementing exercise regimens, not only to control this long-term weight gain, but also as a beneficial maintenance treat-

ment option for patients, especially those with less severe depression or who are coming out of depression.

Dr. Dunner: Informing patients of the high risk of recurrence for people with multiple depressive episodes may encourage adherence in maintenance therapy patients.⁸³ If a patient has had 3 or more depressive episodes, the likelihood is 95% that another depressive episode will occur within the next 2 years.⁸⁴

Dr. Keller: Comparing maintenance treatment for depression to that for diabetes or hypertension can also help encourage patients to take their medication to stay well, rather than just to get well. Also, patients should monitor their own moods using established self-rating scales such as the BDI,¹⁸ PHQ-9,¹⁹ and the QIDS.²⁰ By self-monitoring their moods, patients will know firsthand exactly how they are doing, which can help them evaluate the course of their depression.

Dr. Dunner: If patients want to stop pharmacotherapy, I suggest their medication be tapered and self-monitoring of their moods introduced to help them identify the return of symptoms. Self-monitoring can help patients get back on medication treatment in a timely manner and realize that lowering the dose may cause some return of symptoms. Even if patients have achieved remission, continued self-monitoring is necessary to ensure that they remain euthymic.

Conclusion

Dr. Dunner: To conclude, some patients may experience recurring depressive episodes throughout their lives unless maintenance therapy is used to prevent relapse. Treatment should include both psychotherapy and pharmacotherapy, and medication dosage typically should not be decreased after remission. Physicians should monitor patients for comorbidities, tachyphylaxis, and nonadherence to treatment.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lithium (Eskalith, Lithobid, and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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

Faculty disclosure: In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME article were asked to complete a statement regarding all relevant financial relationships between themselves or their spouse/partner and any commercial interest (i.e., a proprietary entity producing health care goods or services consumed by, or used on, patients) occurring within the 12 months prior to joining this activity. The CME Institute has resolved any conflicts of interest that were identified. The disclosures are as follows: **Dr. Dunner** has received grant/research support from Eli Lilly, Pfizer, GlaxoSmithKline, Wyeth, Bristol-Myers Squibb, Forest, Cyberonics, Janssen, Novartis, and Otsuka; is a consultant or advisory board member for Eli Lilly, Pfizer, GlaxoSmithKline, Wyeth, Bristol-Myers Squibb, Concept, Janssen, Novartis, Shire, Somerset, Otsuka, Siemens, and Roche; and is on the speaker's bureau for Eli Lilly, Pfizer, GlaxoSmithKline, Wyeth, Forest, Cyberonics, and Sanofi-Aventis. **Dr. Blier** is President of Medical Multimedia, Inc.; is a contract employee of Forest, Janssen, and Steelbeach Productions; is a consultant for Biovail, Eli Lilly, Forest, Janssen, Lundbeck, Organon, Sepracor, Wyeth, Sanofi-Aventis, and Pfizer; is on the speaker's bureau for Cyberonics, Eli Lilly, Forest, Janssen, Lundbeck, Organon, and Wyeth; and has received grant/research support from Eli Lilly, Forest, Janssen, Lundbeck, Mitsubishi, Organon, Wyeth, and AstraZeneca. **Dr. Keller** is a consultant for or has received honoraria from Collegium, Cypress Bioscience, Cyberonics, Eli Lilly, Forest, Janssen, Organon, Otsuka, Pfizer, Pharmastar, Sepracor, Vela, and Wyeth; has received grant/research support from Eli Lilly, Forest, Pfizer, and Wyeth; and is on the advisory boards for Abbott, Bristol-Myers Squibb, Cyberonics, Cypress Bioscience, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Novartis, Organon, Pfizer, Sepracor, and Wyeth. **Dr. Pollack** is a consultant for and is on the advisory boards for AstraZeneca, Brain Cells, Bristol-Myers Squibb, Cephalon, Forest, GlaxoSmithKline, Janssen, Jazz, Eli Lilly, Medavante, Neurocrine, Novartis, Otsuka, Pfizer, Predix, Roche, Sanofi, Sepracor, UCB Pharma, and Wyeth; has received grant/research support from Bristol-Myers Squibb, Cephalon, Forest, GlaxoSmithKline, Janssen, Eli Lilly, National Alliance for Research on Schizophrenia and Depression, National Institute on Drug Abuse, National Institute of Mental Health, Pfizer, Sepracor, UCB Pharma, and Wyeth; is on

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