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

This ACADEMIC HIGHLIGHTS section of 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, Rhode Island;* ***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* ***John M. Zajecka****, M.D., from the Depression Treatment Research Center, Rush University Medical Center, Chicago, Ill.*

Financial disclosure appears at the end of the article.

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Major depressive disorder (MDD) is a recurrent or chronic disorder in many patients. Patients who receive inadequate treatment and fail to reach remission are at risk for poor long-term outcomes, including ongoing morbidity and mortality from other psychiatric and medical conditions, impaired psychosocial function, and increased tendency to relapse. While safe and effective treatments exist for major depressive disorder, until recently there was only limited evidence on how to successfully treat patients who do not achieve remission after a single course of antidepressant treatment or who respond but then experience recurrent episodes. A panel of experts convened to address questions about the long-term treatment and prevention of recurrence of MDD.

What Is the Difference Between Continuation Therapy and Maintenance Therapy?

Martin B. Keller, M.D., began the discussion by defining *continuation therapy* as a treatment intended to prevent relapse, that is, to suppress the symptoms of a current episode that has not yet been fully resolved. The typical time frame established for continuation therapy is approximately 4 to 6 months after patients have responded in the acute phase of treatment.[1] In describing continuation therapy studies for MDD, David L. Dunner, M.D., stated that the typical study design is to include patients who responded to an antidepressant during the acute treatment phase and then continue some patients on antidepressant medication and switch others to placebo. Invariably, antidepressant continuation treatment is more effective than placebo,[2–5] illustrating the need for continuation therapy with all treatments, including psychotherapy.[6–9] For example, a review by Keller and Boland[10] 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).[10–15]

Dr. Keller explained that, 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 (Figure 1).[16] According to Hirschfeld,[17] the duration of maintenance therapy is 6 to 24 months. However, in the absence of other, more curative treatment options, Dr. Thase asserted that maintenance therapy may be needed for an indefinite amount of time for certain patients, which in functional terms may translate into lifelong treatment.

What Clinical Characteristics Suggest a Patient Is or Is Not a Candidate for Maintenance Therapy for Major Depression?

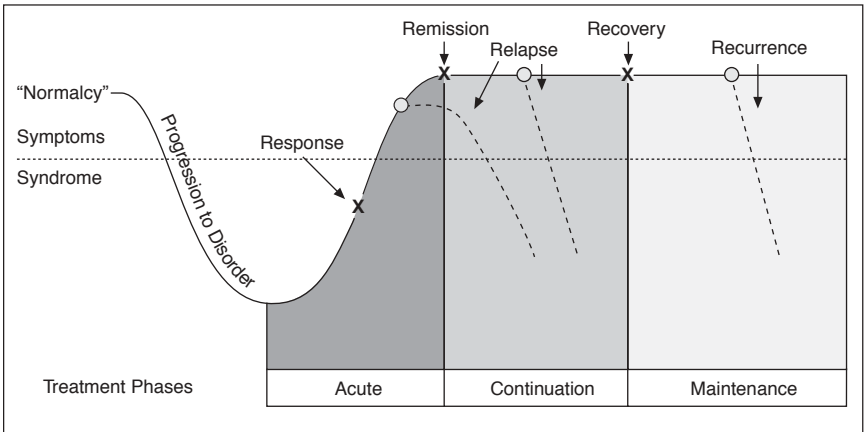
The major characteristics that qualify a patient with major depression for maintenance therapy, as identified by Michael E. Thase, M.D., are the number of prior episodes the patient has had and the frequency of recurrence. Patients who have had 2 episodes within several years or a lifetime history of 3 or more episodes would be likely to show the greatest benefit from longer term, preventive therapy.

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

Study	Drug	Relapse Rate	
		Drug (%)	Placebo (%)
Montgomery et al[11]	Fluoxetine	26	57
Montgomery and Dunbar[12]	Paroxetine	16	43
Doogan and Caillard[13]	Sertraline	13	46
Montgomery et al[14]	Citalopram	11	31
Feiger et al[15]	Nefazodone	17	33

[a]Adapted with permission from Keller and Boland.[10]

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



[a]Reprinted with permission from Kupfer.[16]

Dr. Keller agreed and clarified that anyone who has had 2 lifetime episodes in addition to the current episode be thought of as a candidate[1]; however, he recommended using good judgment when determining patients' eligibility for maintenance therapy. John M. Zajecka, M.D., stated that only patients who have achieved remission should be considered for maintenance treatment. The experts agreed with Dr. Zajecka and went on to discuss other clinical characteristics supporting maintenance therapy candidacy, including residual symptoms, ongoing psychosocial stressors, pregnancy, and seasonal affective disorder.

Residual Symptoms

Patients who have attained remission but are not asymptomatic, that is, 1 or 2 symptoms still persist, are at a high risk for relapse and should continue to receive maintenance treatment, according to Dr. Keller.[18,19] These persistent symptoms, or residual symptoms, in major depression may include difficulties in concentrating, sleep disturbances, subtle decreases in energy levels, and minor persistent anxiety symptoms. Elaborating on this concept, Dr. Thase said that 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.[20–22] As an example, Pierre Blier, M.D., cited Judd et al.,[23] who assessed 96 first-episode patients over 12 years based on the presence or absence of residual symptoms. Results indicated that patients with residual subthreshold symptoms had a more severe course of illness, had more chronic depressive episodes, and had relapse/recurrence rates 3 times those of asymptomatic patients. Therefore, Dr. Thase emphasized that proper assessment of patients' residual symptoms is necessary to treat depression during the maintenance phase of therapy and optimize patient outcome. Dr. Dunner also advocated using evidence-based assessments rather than oral evaluations to help clinicians accurately determine patients' symptom severity; without rating scales, patients have a tendency to tell the physician that they "feel fine."

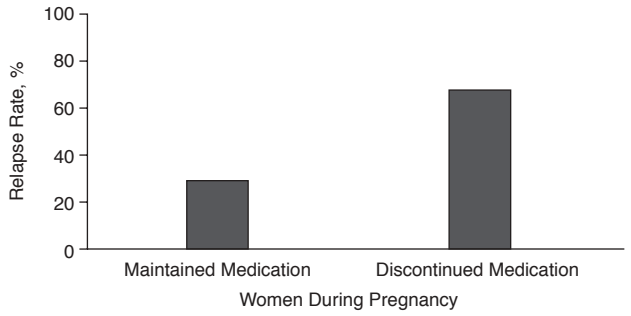
Ongoing Psychosocial Stressors and Comorbidities

Mark H. Pollack, M.D., asked whether treatment should be continued in patients who meet the criteria for remission but for whom life situations or life events continue to be chaotic or stressful. Dr. Dunner maintained that ongoing stressors may negatively affect patients' daily functioning. Simons et al.[24] found that patients who score high on cognitive measures may recognize negative life events more readily and may have a lower threshold for coping with such events than patients who do not score high on cognitive measures. Although no correlation was found between these life events and the onset of depression, results showed that the perceived impact of life stressors may initiate or prolong depressive episodes for patients who have been diagnosed with depression. Additionally, Dr. Keller referred to the Camberwell Collaborative Depression Study,[25] which 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 added that comorbid medical illnesses are also ongoing stressors, and patients who have illnesses that put them at risk for depression should be considered for maintenance therapy as well. For example, patients who have cardiovascular disease, cancer, and diabetes have a higher risk of developing depression and therefore are also at higher risk for relapse.[26–29] Also, anxiety commonly presents with depression,[30] as

Dr. Pollack stated, and monotherapy may not be effective in treating both disorders in maintenance therapy.[31] Instead, medication augmentation, such as antidepressants in combination with benzodiazepines, may prevent or decrease the risk of relapse in this population.[30,31] Additionally, Dr. Keller mentioned that patients who are in their second episode and have poor symptom control or concomitant substance abuse are candidates for maintenance treatment as well.[32]

Figure 2. Comparison of Relapse Rates for Pregnant Women Who Maintained or Discontinued Maintenance Antidepressant Medication[a]



[a]Data from Cohen et al.[43]

Seasonal Affective Disorder

Seasonal affective disorder is a recurrent depression, according to Dr. Dunner, and is a treatment target for maintenance therapy instead of annual treatment. Dr. Thase approximated that 15% to 25% of people with MDD have a fall-winter pattern of episode recurrence, making this a prevalent type of depression.[33] Evidence[34] suggests that phototherapy and other chronobiological interventions may have added value for treating patients with this disorder.[35] Dr. Thase stated that light boxes can be purchased at fairly reasonable prices relative to medication cost. Phototherapy may be more effective in people with mild symptomatology, while pharmacotherapy may be necessary to treat patients with more severe presentations of the illness.[36] To prevent relapse or suicidal tendencies, Dr. Dunner remarked that he would provide maintenance pharmacotherapy to patients with more severe mood disorders rather than rely on them to report annually for phototherapy treatment. Concerning pharmacotherapy, bupropion has been shown to be efficacious and is approved to treat seasonal affective disorder[37]; however, study results of other medications have shown variability in effectiveness.[38–42]

Dr. Zajecka stressed that 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, pharmacotherapy, or augmentation, depending on the individual patient. Further, Dr. Thase said that physicians should provide ongoing, supportive monitoring to their patients to minimize the risk of full-blown relapses.

Who Is *Not* a Candidate for Maintenance Therapy?

Dr. Zajecka suggested that it might be 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 be on medication. Although any patient may be at risk for relapse, Dr. Zajecka recommended that it is reasonable to discontinue treatment in these particular examples, keeping these patients under observation, and being prepared to treat them again if relapse occurs.

Pregnancy

Dr. Dunner used the previous comment to segue into the next topic of discussion: What are the teratogenic risks of long-term treatments for major depression? Dr. Thase stated that the risk of a recurrence of depression both during and following pregnancy is substantial for the mother while the risk of teratogenicity for the fetus is uncertain. For example, Cohen et al.[43] showed that 68% of women who were euthymic at conception and discontinued antidepressant medication during pregnancy relapsed (Figure 2), with a majority relapsing in the first trimester. Another study[44] indicated that 42% of women restarted an antidepressant during pregnancy, suggesting a high level of symptom severity. 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 agreed and emphasized 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.[45–49]

Dr. Dunner stated that there is a lack of data for the use of antidepressants during pregnancy and that, generally, there is no syndrome associated with the use of these agents.[48,50,51] However, one study[52] 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. In a peer-reviewed editorial,[53] Dr. Blier criticized these findings and explained that when the entire pregnancy was examined, no significant association was reported, illustrating the lack of evidence for SSRIs as a teratogenetic risk for pulmonary hypertension. Further, evi-

dence[54,55] that paroxetine causes cardiac malformations in infants has varied. Dr. Keller also concluded that no adverse effects to the fetus have been found with fluoxetine, indicating that this medication may be safe to treat women during pregnancy.[56] Regardless, Dr. Thase acknowledged that both the mother and father should be informed of any potential risk to the unborn child.

What Are the Data Regarding Maintenance Pharmacotherapy for MDD?

Pharmacotherapy Data

Pharmacotherapeutic agents have been shown to be effective in treating patients with recurrent depression (Table 2).[11,57–64] A review by Hirschfeld[57] found that approximately 60% of patients with 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,[11,57,60–64] suggesting prophylactic efficacy of antidepressants in the treatment of recurrent depression.

Dr. Keller cited a progression of studies[65] that he and his colleagues completed beginning with the acute and continuation phases of treatment and leading up to the maintenance phase of pharmacotherapy for patients with recurrent depression. The study[65] enrolled 1096 patients with recurrent depression, which was defined as having had at least 2 depressive episodes in addition to the current one within the past 5 years. The participants were assigned in a double-blind fashion to receive venlafaxine or fluoxetine for 10 weeks during the acute phase of treatment. Those patients who responded and remained well were admitted into the 6-month continuation phase of treatment, again with either venlafaxine or fluoxetine. Patients who maintained a medication response over this period of time were then randomly assigned in a double-blind fashion to receive venlafaxine or placebo for the maintenance phase of treatment, which lasted up to 2 years. During the first year of the maintenance phase of treatment,[65] patients taking venlafaxine had lower rates of recurrent depression as compared with patients on placebo (Figure 3). During the second year,[65] patients who were switched to placebo also had higher rates of recurrence. Dr. Thase added that although he and his colleagues were permitted to use doses up to 300 mg/day of venlafaxine, which is higher than the approved dose for the once-daily formulation, 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 stated that after almost 3 years of treatment, patients may have wanted to discontinue antidepressant medication; however, the risk for relapse seemed to increase over time rather than decrease.

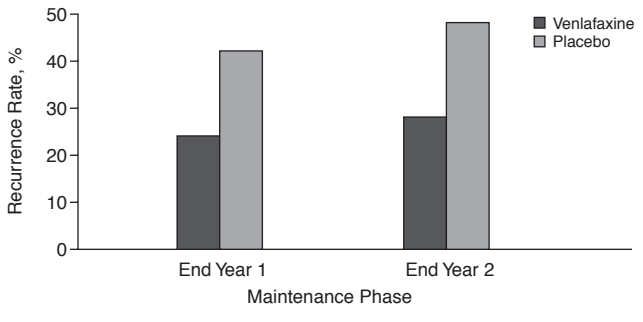
Dr. Keller also cited a study[66] published in 1990 that examined imipramine versus placebo treatment. Again, the definition of recurrent depression involved 2 prior depressive episodes in addition to the current episode over the past 5 years. After 3 years, fewer symptoms recurred in imipramine-treated patients than in patients who switched to placebo (20% and 80%, respectively). Dr. Dunner elaborated on these findings by referring to a 2-year extension[67] of the 3-year study.[66] This study showed again that those patients taking imipramine for more than 3 years, when randomly assigned to treatment with placebo, had a high recurrence rate over the subsequent 2-year period (Figure 4),[66,67] further underscoring the need for patients to remain on maintenance pharmacotherapy to prevent relapse. Additionally, maintenance studies of citalo-

Table 2. Maintenance Studies of Recurrence Rates of Antidepressants Versus Placebo[a]

Study	Drug	Recurrence Rate	
		Drug (%)	Placebo (%)
Kane et al[58]	Imipramine	66	100
Prien et al[59]	Imipramine	33	65
Robinson et al[60]	Phenelzine	29	81
Old Age Depression Interest Group[61]	Dothiepin	40	60
Kocsis et al[62]	Desipramine	11	52
Montgomery et al[11]	Fluoxetine	26	57
Terra and Montgomery[63]	Fluvoxamine	13	35
Keller et al[64]	Sertraline	6	23

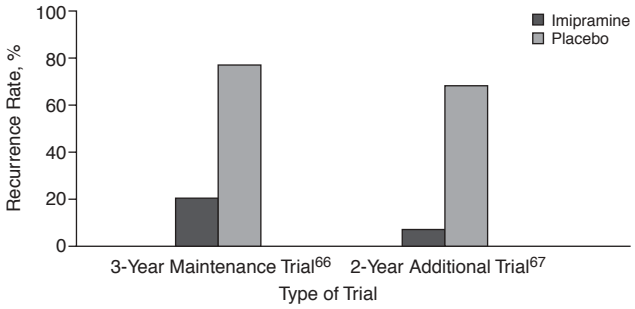
[a]Adapted with permission from Hirschfeld.[57]

Figure 3. Comparison of Relapse Rates for Maintenance Venlafaxine Versus Placebo for Patients With Recurrent Depression[a]



[a]Data from Keller et al.[65]

Figure 4. Comparison of Recurrence Rates for Maintenance Imipramine Versus Placebo for Patients With Recurrent Depression[a]



[a]Data from Frank et al.[66] and Kupfer et al.[67]

pram[68] and sertraline[69] found that patients who remained on medication had a longer time to depressive episode recurrence and fewer recurrences than those who were randomly assigned to placebo.

Reinitiation of Medication

Data[70] on panic disorder have suggested that many patients who stop their medication may relapse or have recurrent symptoms, but will respond when the treatment is restarted, albeit on a slower time course than during initial treatment. Regarding major depression, Dr. Pollack asked about the prospect of response to medication readministration once patients have responded to a particular drug and have subsequently discontinued this pharmacotherapy. Dr. Zajecka noted that 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 et al.[71] found that, of patients who relapsed on placebo and were reinitiated into fluoxetine therapy, 62% responded. Thus, patients are likely to respond to medication reinitiation. In a study[72] of retreatment conducted by Dr. Thase's 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 depressive episodes was greatly reduced because of early detection. Dr. Blier agreed that early detection is important, because remission could be more difficult to attain later if the patient is allowed to continue in the relapsed state for some time. Dr. Blier and colleagues[73] also found that patients who achieved remission, discontinued their medication, and subsequently relapsed responded well to medication readministration and were able to achieve remission for the second time.

Atypical Depression

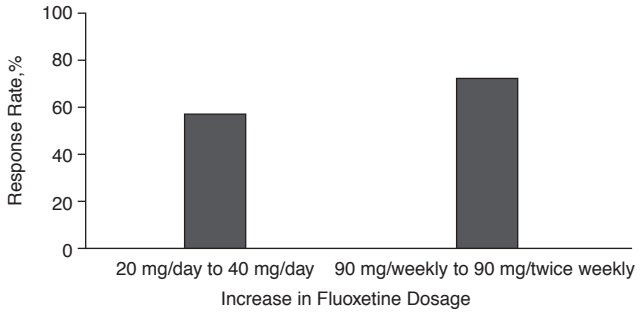
Dr. Dunner then focused on a subtype of depression and asked the panel if atypical depression is different from other forms of depression regarding the need for maintenance therapy. In response, Dr. Thase cited a study conducted by Stewart et al.[74] that examined patients with atypical depression who achieved remission for at least 6 months with either phenelzine or imipramine and who were then randomly assigned to either continue their current medication or receive placebo for an additional 6 months. Phenelzine, a monoamine oxidase inhibitor (MAOI), showed a clear protective effect 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 patients 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.

What Duration and Dose of Maintenance Pharmacotherapy Should Be Used?

Dr. Dunner stated that, in his understanding, the average duration of antidepressant treatment in the United States remains below that recommended by the Agency for Health Care Policy and Research (AHCPR) Practice Guidelines[75,76] even though these guidelines were developed over almost a decade ago.[77] According to the AHCPR Practice Guidelines 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. Dr. Dunner noted that physicians, as a group, are not closely adhering to the established treatment guidelines when using pharmacotherapy for depression.

Dr. Zajecka stated that clinicians should perceive depression as potentially being a life-long illness in many patients rather than like illnesses that can usually be cured with a single, short course of treatment such as an antibiotic. Dr. Dunner inquired whether a 20-year-old female college student with recurrent depressive episodes should take an antidepressant forever. Dr. Thase distinguished between "forever" and "indefinitely." In the future, treatments that target the altered pathologic mechanisms of recurrent depression may be available

Figure 5. Response Rates to an Increase in Fluoxetine Dosage Following Relapse in Patients With Recurrent Depression[a]



[a]Data from Schmidt et al.[80]

and may have a more curative effect than the present medications, which suppress illness activity. Future treatments may be able to be stopped with fewer hazards than the currently available pharmacotherapeutic options. Dr. Thase recommended that patients be advised to take treatment one year at a time.

Same Dose That Achieved Remission

According to Dr. Keller, current evidence[10,66,67,78,79] suggests maintaining patients on the same dose of medication that was necessary to achieve recovery or remission in the acute episode. For example, Frank et al.[79] found that full-dose maintenance treatment over 3 years was more effective than half-dose maintenance treatment in patients with recurrent depression (mean survival time 135.17 weeks versus 74.94 weeks, respectively). Because of the absence of a large study using first-line treatments that provides evidence of equal efficacy after lowering the dosage of medication, Dr. Keller recommended maintaining the original pharmacotherapeutic dose to promote optimal patient outcome.

Higher Dosages

Dr. Dunner cited a study[80] in which patients with depression were administered 20 mg/day of fluoxetine for 13 weeks. Responders to this medication were continued on 20 mg/day of fluoxetine or switched to 90 mg/week of fluoxetine or placebo for 25 weeks of continuation therapy. Patients who relapsed during this phase of treatment had their doses of fluoxetine increased in the following manner: patients on placebo went to 20 mg/day of fluoxetine, patients on 20 mg/day increased to 40 mg/day, and patients on 90 mg/week increased to 90 mg/twice a week. Patients whose medication was increased had substantial response rates (Figure 5). Dr. Blier noted that as pharmacotherapy is prolonged, increases rather than decreases in drug dosage may be necessary to elicit favorable outcomes for patients.

What Are the Data Regarding Maintenance Psychotherapy?

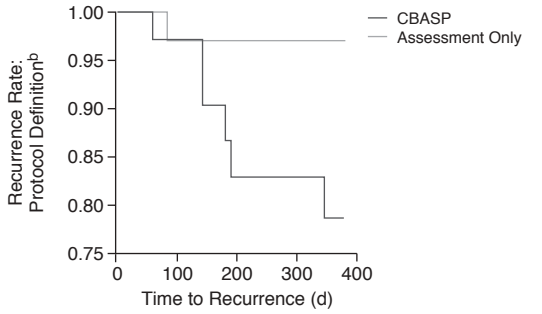
Psychotherapy Data

Dr. Keller explained 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); to use medication alone is insufficient treatment.[19] A 16-month maintenance study[6] found that patients receiving cognitive therapy plus antidepressants had significantly better outcomes on psychological symptoms (guilt, self-esteem, and hopelessness) and psychosocial functioning (dependence, interpersonal behavior, and friction) than those patients who received regular clinical management plus antidepressants.

Dr. Zajecka noted that CBT in the early phases of treatment may prevent relapse, even in patients who discontinue their medication.[81,82] Dr. Keller cited a 12-week study[83] that used a modified form of CBT called cognitive-behavioral analysis system of psychotherapy (CBASP). The results showed that patients randomized to CBASP plus pharmacotherapy had a greater improvement in psychosocial functioning and higher remission rates than patients who received pharmacotherapy or psychotherapy alone in the acute phase. Those patients who achieved full or partial remission were admitted into the 16-week continuation phase of treatment.[84] Again, 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%). Those patients who continued to maintain remission were then randomized to CBASP or assessment only over the 1-year maintenance phase of treatment.[7] Patients in the CBASP group had significantly fewer recurrences ($p \leq .03$) than those patients in the assessment group (Figure 6), showing the efficacy of maintenance psychotherapy in the absence of medication. Additionally, Dr. Keller stated that 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.

Another maintenance study[8] of CBT after pharmacotherapy discontinuation showed that at the 2-year follow-up, patients who received CBT supplemented with lifestyle modification or well-being therapy had significantly lower levels of residual symptoms as compared with patients who only received clinical management. Further, patients in the CBT group also had a lower relapse rate (25%) than the clinical management group (80%). In the

Figure 6. Comparison of Recurrence Rates for Maintenance CBASP Versus Assessment Alone Using Protocol Definition for Patients With Recurrent Depression[a]



[a]Reprinted with permission from Klein et al.[7]
[b]Protocol definition of recurrence = HAM-D-24 score of ≥ 16 on 2 consecutive visits, a diagnosis of MDD according to the DSM-IV, and confirmation by the site's senior investigator on the basis of a clinical interview.
Abbreviations: CBASP = cognitive-behavioral analysis system of psychotherapy; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition; HAM-D = Hamilton Rating Scale for Depression; MDD = major depressive disorder.

6-year follow-up of the same patients, Fava et al.[9] still reported lower relapse rates for the CBT group (40%) than the clinical management group (90%), suggesting that maintenance CBT offers a valid, nonpharmacotherapeutic alternative to the long-term use of antidepressants. Dr. Keller and Dr. Blier concluded that when all of the data are examined as a whole, compelling evidence exists for the value of psychotherapy.

Dr. Thase noted that Fava et al.[85,86] developed personal well-being therapy, a type of therapy based on Ryff's multidimensional model of psychosocial well-being,[87] which focuses on autonomy, personal growth, environmental mastery, purpose in life, positive relations, and self-acceptance. Fava et al.[85,86] showed that well-being therapy reduced residual symptoms, decreased the risk of relapse, and facilitated the subsequent withdrawal of antidepressant medications. Another study[88] 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.

Dr. Thase pointed out that an implicit assumption exists that all psychotherapies are the same. However, in a maintenance study,[89] the amount of time that the psychotherapist spent actually performing interpersonal psychotherapy (IPT) with patients during the maintenance phase of treatment was directly associated with whether IPT was efficacious for relapse prevention. When the psychotherapy had degenerated into supportive conversation and 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 very good preventive treatment or a noneffective treatment based on the quality and focus of the therapy. The experts agreed that finding qualified psychotherapists is key to successful outcomes.

Implementing Psychotherapy

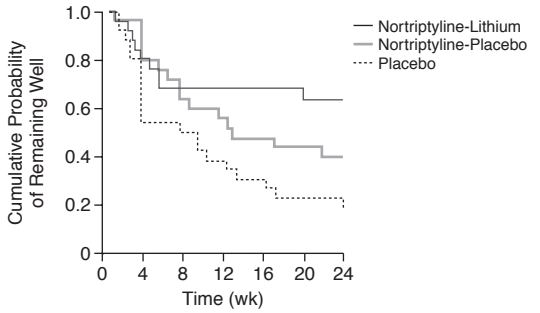
Although the discussants recognized the efficacy of quality psychotherapy, Dr. Pollack observed that the accessibility of these interventions may vary outside specialized treatment centers. Dr. Keller stated that although finding psychotherapists who specialize in CBT or other modified forms of psychotherapy may be difficult, implementing these interventions into patients' treatment regimens is still the ideal treatment. As a solution to finding specialized psychotherapists, Dr. Dunner recommended the Web site academyofct.org, through which cognitive-behavioral psychotherapists trained by Aaron Beck may be located. Dr. Thase suggested that 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. Keller also noted that 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. Blier cautioned that the cost of psychotherapy may be a problem for patients. For example, a 1-hour session of CBT may amount to the cost of a 1-month prescription for an antidepressant, which may deter some patients from participating in this treatment option. As a possible alternative if cost or location presents a problem, Dr. Thase noted that Internet-based or telephone-based cognitive-behavioral psychotherapies have been shown to be efficacious for some patients.[90–95] However, online interventions should not be used to replace psychotherapy administered by an actual person, if that is an available option.

What Are the Data Regarding Maintenance Electroconvulsive Therapy?

All of the experts agreed that maintenance electroconvulsive therapy (ECT) should only be used as a treatment of last resort, that is, after patients have failed to respond to pharmacotherapy and psychotherapy.[96] Dr. Thase stated that although ECT can be dramatically effective and lifesaving, it is also costly and can be very life disrupting; thus, its place as a third-

Figure 7. Pharmacotherapy Efficacy Following Electroconvulsive Therapy[a]



[a]Reprinted with permission from Sackeim et al.[100]

or fourth-line treatment for most forms of depression is generally well justified. A review by Dr. Zajecka[97] reported response rates of 50% to 60% with ECT for treatment-resistant patients; however, this treatment may be associated with memory loss and high relapse rates. The Consortium for Research in Electroconvulsive Therapy (CORE) study[98] found that maintenance ECT was as effective—but no more effective—than the combination of preventive antidepressant and mood stabilizer treatment for patients with recurrent depression. The major criticism of the CORE study is that the patients included had not failed on previous prevention medication strategies. Therefore, the CORE study may present medication maintenance in a more favorable light than is usually the case when considering maintenance ECT.

Dr. Zajecka cited a small study[99] in which 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 they have remitted. Also, Dr. Dunner pointed out that Sackeim et al.[100] showed that the combination of nortriptyline and lithium following ECT treatment was superior to placebo or medication monotherapy in preventing relapse (Figure 7).

Additional Considerations for Maintenance Therapy

Comorbid Substance Use Disorders

Dr. Blier noted that one factor that is often overlooked in maintenance trials is the issue of substance use or alcohol use or abuse. In general, patients with dual diagnosis are not admitted into acute treatment trials because this comorbidity can decrease the remission rate. For example, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[101] found an overall remission of 28%. However, in the patients with substance use or alcohol abuse, the remission rate was only 20%. Therefore, substance abuse is an important issue in treating recurrent depression because substances can be a contributing factor for relapse. Yet, this comorbidity is often neglected when treating patients with recurrent depression. Dr. Zajecka agreed that clinicians need to remain cognizant of the high comorbidity between affective disorders and substance use disorders.

Tachyphylaxis or Recurrence

Dr. Dunner next engaged the group on the topic of tachyphylaxis, or what has been called drug tolerance or the "poop-out" phenomenon, and asked how to deal with this confounding situation. Dr. Zajecka explained that when the SSRIs came on to 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. This phenomenon may be theoretically 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).[102] Also, patients may respond to adjunctive noradrenergic or dopaminergic agents in addition to an SSRI.

Dr. Blier agreed with Dr. Zajecka and noted that after sustained administration of an SSRI, the atonic activity of the norepinephrine neurons in the locus ceruleus decreases quite markedly—from 30% to 70%, depending on the drug.[103] Dr. Blier and colleagues (B. Guiard, Ph.D.; M. El-Mansari, Ph.D; P. Blier, M.D., Ph.D., unpublished data, 2006) have recently completed studies showing that the serotonin neurons exert an inhibitory action on dopaminergic neurons in the ventral tegmental area (VTA). For example, when lesions are present in the serotonin neurons, the VTA-dopamine neurons increase their firing, so there is a braking action of serotonin on the VTA. If physicians administer an SSRI, the dystonic inhibitory effect is increased, which decreases the dopaminergic tone. Therefore, Dr. Blier concurred that the way Dr. Zajecka proposed managing the poop-out phenomenon is consistent with the neurobiological data.[103–106]

Table 3. Reasons Patients May Become Nonadherent During Maintenance Pharmacotherapy

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

Dr. Keller mentioned that he and other researchers invented a tachyphylaxis rating scale because one did not exist that had validated psychometric properties.[107] The experts agreed that tachyphylaxis is a presentation of anhedonia, a lack of motivation, and loss of libido, but Dr. Dunner concluded that 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 TCAs[66]; studies have found that about 1 in 4 patients who receive maintenance treatment for major depression experience a recurrence.[107] 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 suggested that the easiest explanation for tachyphylaxis is that the active medication has been attributed to be the agent of maintaining the patient's improvement, when in reality patients remitted spontaneously or responded to the placebo effect. Dr. Thase also suggested that the phenomenon could sometimes be due to patients not being as adherent to their medication regimen as they say that they are.

Addressing Nonadherence in Patients

Nonadherence is an important consideration in maintenance therapy, the experts agreed. Dr. Blier explained that approximately 50% of patients stop their medication prematurely and do not go beyond 3 months of their treatment.[32,108,109] He emphasized that physicians should work to enhance patients' comfort level to ensure they adhere to treatment recommendations. Dr. Dunner agreed and asked the expert panel to elaborate on reasons why patients may become nonadherent at this phase of treatment (Table 3). The obvious factors, said Dr. Keller, are that patients believe that they will remain euthymic off medication, that the medication does not produce the desired outcomes, or that serious adverse events or side effects occurred. Dr. Thase noted that 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.[110] 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 added that comorbid substance abuse may be a contributing factor to medication discontinuation, as well.

Dr. Dunner cited weight gain as another factor for medication discontinuation.[110] Dr. Thase stated that 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, they recognize a substantial weight gain. Dr. Blier recommended implementing exercise regimens not only to control this long-term weight gain but also as a beneficial maintenance treatment option for patients with depression.[111] For example, neurological experiments have shown that exercise has increased neurogenesis in animals.[112,113]

To encourage adherence in maintenance therapy patients, Dr. Dunner recommended informing patients of the high risk of recurrence for people with multiple depressive episodes.[114] 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.[115] Dr. Keller suggested comparing maintenance treatment for depression to that for diabetes or hypertension so that patients will be encouraged to take their medication to stay well, not just to get well. Also, patients should monitor their moods using established self-rating scales such as the Beck Depression Inventory (BDI),[116] the Patient Health Questionnaire (PHQ-9),[117] and the Quick Inventory of Depressive Symptomatology (QIDS).[118] By self-monitoring their moods, patients will know first-hand exactly how they are doing, which can help them evaluate the course of their depression. If patients want to stop pharmacotherapy and their medication is tapered, self-monitoring of their moods will help them identify the return of symptoms. Therefore, patients will be able to go back on the medication in a timely manner and also realize that lowering the dose may cause some return of symptoms. Dr. Dunner also stated that even if patients have achieved remission, continued self-monitoring is necessary to ensure that they remain euthymic.

Conclusion

The experts concluded that recurrent depression is potentially a long-term or even life-long illness for many patients, and maintenance therapy is designed to prevent relapse in patients with recurrent depression. Candidates for maintenance therapy include patients who have achieved remission and have had 2 or more lifetime episodes, especially if patients have ongoing psychosocial stressors, residual symptoms, comorbid illnesses, or severe depressive episodes. Maintenance pharmacotherapy data strongly support the use of antidepressants at the dosage that helped the patient achieve remission. Other effective maintenance treatment interventions include psychotherapy, especially cognitive-behavioral therapy, and in some extreme cases, electroconvulsive therapy.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), desipramine (Norpramin 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) 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, Corcept, 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 or 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 the speaker's bureau for Bristol Myers Squibb, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Pfizer, Solvay, and Wyeth; and has equity in Medavante. **Dr. Thase** is a consultant for or is on the advisory boards for AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, GlaxoSmithKline, Janssen, Neuronetics, Novartis, Organon, Sepracor, Shire, and Wyeth; and is on the speaker's bureau for AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, GlaxoSmithKline, Organon, Sanofi-Aventis, and Wyeth. **Dr. Zajecka** has received grant/research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, McNeil, Novartis, PamLab, and Somaxon; is a consultant for or is on the advisory boards for Abbott, Biovail, Bristol-Myers Squibb, Eli Lilly, Otsuka, PamLab, and Wyeth-Ayerst; and is on the speaker's bureau for Abbott, AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, Pfizer, GlaxoSmithKline, and Wyeth-Ayerst. This article has been peer-reviewed to make sure it is evidence-based and has fair balance.

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