Tachyphylaxis in Unipolar Major Depressive Disorder

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Background: Major depressive disorder is usually a recurring illness, and maintenance treatment is used to forestall or prevent recurrent episodes of depression. This study describes recurrence of major depression despite maintenance pharmacotherapy, termed *tachyphylaxis*.

Method: The study sample consisted of 103 subjects who participated in the NIMH Collaborative Depression Study, a multicenter longitudinal observational study of the mood disorders. Subjects diagnosed with unipolar major depressive disorder according to Research Diagnostic Criteria were enrolled from 1978–1981 and prospectively followed for up to 20 years. As an observational study, treatment was recorded but not controlled by anyone connected with the study. Subjects were selected for the present study if at some point during follow-up they received antidepressant medication for treatment of an episode of major depressive disorder, recovered from this episode, and subsequently received maintenance pharmacotherapy. Some subjects were successfully treated for multiple episodes of major depressive disorder and then received maintenance medication after each of these episodes, resulting in multiple maintenance treatment intervals. Data were collected using the Longitudinal Interval Follow-Up Evaluation, and mixed-effects logistic regression was used to test the association of sociodemographic and clinical variables with tachyphylaxis.

Results: For the 103 subjects, there were 171 maintenance treatment intervals in which a subject received maintenance pharmacotherapy after having recovered from an episode of major depressive disorder. The median duration of maintenance treatment was 20 weeks. Tachyphylaxis occurred during 43 (25%) of these 171 maintenance treatment intervals. The subtype of melancholic (endogenous) major depressive disorder significantly elevated the risk of tachyphylaxis during the subsequent maintenance treatment interval.

Conclusions: Despite the use of maintenance pharmacotherapy, major depression recurs in a considerable number of patients. Improved prophylaxis for these patients requires other treatment strategies based upon a greater understanding of recurrence.

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Major depressive disorder is usually a recurring illness, with each episode of major depression increasing the probability of yet another episode.[1] To forestall and prevent these recurrences of depression, treatment guidelines[2] suggest maintenance therapy after the episode of major depression has resolved. This recommendation is based upon the demonstrated success of maintenance treatment in numerous randomized controlled trials.[3–8]

Unfortunately, despite the use of full doses of maintenance medication, patients sometimes suffer a recurrence of major depression. This phenomenon has been variously termed antidepressant *tachyphylaxis*, *tolerance*, or *poop-out*.

The frequency of tachyphylaxis is not clear. Within randomized controlled trials of maintenance therapy lasting up to 3 years, 9% to 57% of subjects suffered a recurrent episode of major depression while receiving active treatment.[9] Although these treatment trials have provided indispensable information about the efficacy of maintenance treatment, their protocols have typically excluded mildly depressed patients, suicidal or psychotic patients,

patients with comorbid illnesses, and patients requiring concomitant medications. As a result, the findings of randomized controlled trials do not necessarily generalize to the majority of individuals with major depressive disorder, who are excluded from such treatment trials.[10–12]

For patients treated in the community, information about recurrence of major depression during maintenance treatment is important, given the emphasis placed upon maintenance treatment within practice guidelines[2] and the fact that major depressive disorder is highly prevalent,[13] highly recurrent,[1] and associated with substantial disability[14] and mortality.[15] The present analyses were conducted to provide additional data regarding tachyphylaxis and to identify risk factors associated with this phenomenon.

The data presented here come from the ongoing National Institute of Mental Health-Collaborative Program on the Psychobiology of Depression (Collaborative Depression Study [CDS]). The CDS is a prospective, longitudinal, observational investigation of the course of illness in the mood disorders[16] and is well suited to examine tachyphylaxis. The sample of subjects with major depressive disorder is large, diagnostically homogeneous, and well characterized by standardized diagnostic criteria and standardized assessments for follow-up. Level of psychopathology and treatment with antidepressant medication are both assessed frequently throughout the lengthy follow-up, and multiple episodes of major depression have been observed in their entirety for many subjects.

METHOD

Overview

Tachyphylaxis was examined in subjects who recovered from the intake episode of major depressive disorder and at some point during follow-up (1) received antidepressant medication for treatment of a recurrent episode of major depressive disorder, (2) recovered from this episode, and (3) subsequently received maintenance pharmacotherapy. Some subjects were successfully treated for multiple episodes of major depression and received maintenance medication after recovering from each of these episodes; this resulted in multiple maintenance treatment intervals for certain subjects.

Subjects

From 1978 through 1981, inpatients and outpatients with mood disorders were enrolled into the CDS at academic medical centers in Boston, Mass.; Chicago, Ill.; Iowa City, Iowa; New York, N.Y.; and St. Louis, Mo. Inclusion criteria included age of at least 17 years, intelligence quotient greater than 70, ability to speak English, white race (genetic hypotheses were tested), and no signs of a mood or psychotic disorder secondary to a general medical condition. The study was approved by an institutional review board at each site, and each subject provided written informed consent after receiving a complete description of the study.

Among the 955 patients enrolled in the CDS, there were 431 in an episode of major depressive disorder, with no underlying minor depressive disorder or chronic intermittent depressive disorder of at least 2 years' duration, and no prior history of mania, hypomania, or schizoaffective disorder. Of these 431 subjects, 103 recovered from the intake episode of unipolar major depressive disorder and, at some point during follow-up, suffered at least 1 recurrent episode of major depressive disorder that was prospectively observed in its entirety, recovered from this episode while receiving antidepressant medication, and then received maintenance pharmacotherapy (defined below). No episodes of mania, hypomania, or schizoaffective disorder were observed in these 103 subjects during follow-up, which lasted up to 20 years.

Assessments

At study intake, current and past psychiatric history was assessed with the Schedule for Affective Disorders and Schizophrenia-regular version.[17] Diagnoses were then made according to Research Diagnostic Criteria (RDC).[18]

Follow-up assessments were completed every 6 months for the first 5 years of the study and yearly thereafter. At these assessments, raters administered the Longitudinal Interval Follow-Up Evaluation (LIFE),[19] which is a semistructured instrument that measures the severity of psychopathology on a weekly basis. For major depressive disorder, severity of psychopathology is quantified on a 6-point scale called the "psychiatric status rating" (PSR). A PSR of 1 corresponds to no symptoms. A PSR of 2 corresponds to 1 or 2 symptoms of a mild degree, with no impairment of functioning. A PSR of 3 corresponds to moderate psychopathology considerably less than that meeting the full criteria for a major depressive episode, with no more than moderate impairment in functioning. A PSR of 4 denotes marked symptoms not meeting the full criteria for a major depressive episode, with major impairment in functioning. A PSR of 5 corresponds to symptoms meeting the full criteria for a major depressive episode, and a PSR of 6 indicates full criteria for a major depressive episode along with psychosis or extreme impairment in functioning. The specific wording of the LIFE items, rater qualifications, and interrater reliability of the PSRs have been previously reported.[19] At each interview, the rater assigned a PSR for each week of the interval, starting from the time of the last interview. To accomplish this, the rater first identified chronological anchor points such as holidays, birthdays, and anniversaries to assist the subject in remembering those times when significant clinical improvement or deterioration occurred. Whenever possible, corroborative data were obtained from medical records and informants.

Table 1. Composite Antidepressant (CAD) Scale for Selected Antidepressants

	CAD Scores[a]			
Antidepressant	1	2	3	4
Bupropion, mg	1–149	150–299	300–449	≥ 450
Citalopram, mg	1–19	20–39	40–59	≥ 60
Fluoxetine, mg	1–10	11–20	21–30	≥ 31
Imipramine, mg	1–99	100–199	200–299	≥ 300
Nefazodone, mg	1–88	89–244	245–399	≥ 400
Paroxetine, mg	1–19	20–39	40–59	≥ 60
Phenelzine, mg	1–29	30–59	60–74	≥ 75
Sertraline, mg	1–49	50–100	101–199	≥ 200
Trazodone, mg	1–199	200–399	400–599	≥ 600
Venlafaxine, mg	1–108	109–241	242–374	≥ 375

[a]The CAD scores summarize the daily dose of somatic antidepressant treatment for each week on an ordinal scale. Ratings from 1 to 4 are assigned for each week, representing the daily dose received for that week. A CAD score of zero is assigned for a week in which no somatic treatment is provided, and CAD scores 1 to 4 indicate progressively larger doses.

The analyses reported in this article are based on the PSRs for the 103 subjects with an episode of unipolar major depressive disorder at intake who recovered from this episode and received maintenance pharmacotherapy (defined below). The analyses encompass data for up to 20 years (1040 weeks) of follow-up. *Recovery* was defined as at least 8 consecutive weeks with either no symptoms of major depressive disorder (PSR of 1) or only 1 or 2 symptoms at a mild level of severity (PSR of 2). *Recurrence* was defined as the reappearance of RDC major depressive disorder at full criteria (PSR of 5 or 6) for at least 2 consecutive weeks. Recurrence occurred only after the individual had first recovered from the preceding mood episode. Thus, during an episode of major depressive disorder, the weekly level of psychopathology may have fluctuated from a PSR of 1 to 6. However, a minimum of 8 consecutive weeks at a PSR of 1 or 2 was required for the outcome of recovery. During recovery, the weekly level of psychopathology persisted at a PSR of 1 or 2, and PSR ratings of 3 or 4 were not permitted. Episodes of RDC minor depressive disorder and chronic intermittent depressive disorder were not included in the analyses.

Treatment

This was an observational study in that treatment was not randomly assigned by design and not controlled by anyone connected with the study. In an observational study, the causal relationship between intensity of treatment and level of psychopathology is not known. Thus, for example, some subjects are asymptomatic because they receive high levels of treatment, while other subjects receive high levels of treatment because their symptoms are unremitting. Throughout the follow-up period, the intensity of treatment varied within subjects as well as between subjects.

Information on somatic treatment was collected with the LIFE and corroborated with available medical records. For each week of the study, the rater recorded the mean daily dose of antidepressant treatment. The mean daily dose of somatic antidepressant therapy for each week was then rated on a 5-point scale that yields a composite antidepressant (CAD) score that is intended to summarize the intensity of antidepressant treatment. The scale consists of equivalent daily dose ranges that were established for each antidepressant medication. Table 1 provides examples of CAD scores for various antidepressants, with imipramine representing the tricyclic antidepressants. The rationale and method for deriving the CAD scores have been described previously.[20] Equivalent dose ranges were based upon the expert opinion of the principal investigators and coinvestigators of the CDS, because of the limited randomized controlled trial literature that provides comparisons across graduated doses of the antidepressant medications included in the pharmacopoeia. In summarizing antidepressant treatment across numerous medications, the CAD scale consists of broad classes of treatment intensity that are admittedly somewhat coarse. The CAD scale is similar to other algorithms that have been developed for rating the adequacy of antidepressant treatment.[21]

The CAD algorithms continue to be revised with the introduction of new antidepressants and further clinical experience with existing medications. The algorithms for converting a medication dose into a CAD score include rules for incorporating augmentation medication and polypharmacy. Neither serum medication levels nor pill counts are incorporated into the algorithms, and the CAD scores do not purport to represent biologically equivalent doses. Rather, the CAD scores are a 5-point ordinal scale of treatment intensity, which ranges from 0 to 4. A CAD score of 0 indicates no somatic antidepressant treatment, and CAD scores of 1 to 4 indicate progressively larger doses.

For the purposes of the present study, maintenance pharmacotherapy was defined as a daily dose of antidepressant medication with a CAD score ≥ 3. This intensity of treatment was selected based upon a literature review of maintenance treatment for major depressive disorder. In these randomized controlled studies, the following medications and mean daily doses were used: imipramine 137 mg,[3] imipramine 208 mg,[4] desipramine 232 mg,[5] sertraline 146 mg,[6] and citalopram 34 mg.[8]

Statistical Analysis

The objective of the analyses was to identify risk factors associated with tachyphylaxis. Subjects with and without tachyphylaxis were compared on sociodemographic and clinical variables at intake; continuous variables were compared with t tests, and categorical variables were compared with χ^2 tests. A mixed-effects logistic regression analysis[22,23] examined the association of other clinical (independent) variables with tachyphy-

laxis (dependent variable). Three domains of independent variables were analyzed in separate preliminary mixed-effects models, and those variables with $p < .10$ were then entered into a single reduced model. The mixed-effects models allowed for the use of a multiple number of observations per subject and a varying number of observations between subjects. A 2-tailed α level of .05 was used for each statistical test.

For subjects who recovered from 1 or more prospectively observed episodes of major depressive disorder while receiving antidepressant medication, the time to recovery was calculated using survival analysis.[24] Similarly, time to recurrence while receiving maintenance pharmacotherapy was calculated using survival analysis.

RESULTS

The sample consisted of 103 subjects. The sociodemographic and clinical characteristics of the sample at study intake are displayed in Table 2.

The subjects recovered from 171 episodes of major depressive disorder while receiving an antidepressant medication. Following recovery from these episodes of major depressive disorder, the subjects received maintenance pharmacotherapy. Thus, there were 171 maintenance treatment intervals. The median duration of maintenance treatment was 20 weeks.

Tricyclic antidepressants and related cyclic compounds (including amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, and nortriptyline) were used in 101 (59%) of the 171 maintenance treatment intervals, monoamine oxidase inhibitors (including phenelzine and tranylcypromine) were used in 33 (19%) of the maintenance treatment intervals, selective serotonin reuptake inhibitors (including fluoxetine, paroxetine, and sertraline) were used in 26 (15%) of the maintenance treatment intervals, and other antidepressants (including bupropion, nefazodone, trazodone, or venlafaxine) were used in 11 (6%) of the maintenance treatment intervals. In addition, lithium augmentation was used in 33 (19%) of the 171 maintenance treatment intervals, and antipsychotics were used in 13 (8%) of the maintenance treatment intervals.

Tachyphylaxis occurred during 43 (25%) of the 171 maintenance treatment intervals. From the total sample of 103 subjects, 28 (27%) accounted for all of these episodes of tachyphylaxis. The median time to recurrence for these episodes of tachyphylaxis was 31 weeks; 25% of the episodes of tachyphylaxis occurred within 14 weeks, and 75% occurred within 75 weeks.

Table 3 displays the sociodemographic and clinical characteristics at study intake for the subjects who eventually suffered tachyphylaxis and those who did not. The subjects with tachyphylaxis were significantly younger at study intake, compared to the subjects who did not suffer tachyphylaxis. The 2 groups did not differ significantly on any other characteristic, including family psychiatric history (defined as major depressive disorder, bipolar I disorder, or schizoaffective disorder in any first-degree relative) and comorbid medical illness (defined as any nonpsychiatric medical illness at the time of intake into the study). The finding with regard to age at study intake was examined more closely. The mean (SD) age of subjects at the beginning of the maintenance treatment intervals that resulted in tachyphylaxis (43 intervals) was 40.2 (10.4) years. The mean (SD) age of subjects at the beginning of the maintenance treatment intervals that did not result in tachyphylaxis (128 intervals) was 43.0 (14.6) years. The groups were not independent and were thus compared with a mixed-effects linear regression model,

Table 2. Sociodemographic and Clinical Characteristics at Intake of NIMH Collaborative Depression Study Subjects Who Received Maintenance Pharmacotherapy[a]

Characteristic	Total Group (N = 103)[b]
Sex	
Male	42 (40.8)
Female	61 (59.2)
Marital status	
Married	58 (56.3)
Never married	30 (29.1)
Divorced/separated/widowed	15 (14.6)
Socioeconomic status[c]	
I	5 (4.9)
II	23 (22.3)
III	25 (24.3)
IV	34 (33.0)
V	16 (15.5)
Intake site	
Boston, Mass	9 (8.7)
Chicago, Ill	18 (17.5)
Iowa City, Iowa	33 (32.0)
New York, NY	17 (16.5)
St. Louis, Mo	26 (25.2)
Patient status	
Inpatient	77 (74.8)
Outpatient	26 (25.2)
No. of major depressive episodes prior to intake	
0	32 (31.1)
1	23 (22.3)
2	16 (15.5)
≥ 3	32 (31.1)
Subtype of intake episode of major depression	
Psychotic	8 (7.8)
Endogenous	95 (92.2)
Primary	61 (59.2)
Age, mean (SD), y	39.0 (14.1)
Global Assessment Scale score, mean (SD)	42.7 (12.0)
17-item HAM-D (extracted),[25] mean (SD)	26.3 (6.3)

[a]Subjects met criteria for major depressive disorder at intake and received maintenance pharmacotherapy following recovery from a depressive episode. Some subjects suffered multiple episodes of depression and received maintenance pharmacotherapy for 2 or more episodes.
[b]Values are N (%) unless otherwise indicated.
[c]Hollingshead-Redlich scale; I = highest socioeconomic status, V = lowest socioeconomic status.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, NIMH = National Institute of Mental Health.

Table 3. Sociodemographic and Clinical Characteristics at Intake for Subjects With and Without Tachyphylaxis[a]

Characteristic	Subjects With Tachyphylaxis (N = 28)	Subjects Without Tachyphylaxis (N = 75)	Analysis
Age, mean (SD), y	35 (12)	41 (15)	t = 2.10, df = 58,[b] p = .04
Female, N (%)	19 (68)	42 (56)	χ^2 = 1.19, df = 1, p = .28
Marital status, N (%)			χ^2 = 0.53, df = 2, p = .77
Married/living together	17 (61)	41 (55)	
Never married	8 (29)	22 (29)	
Divorced/separated/widowed	3 (11)	12 (16)	
Socioeconomic status,[c] N (%)			χ^2 = 4.97, df = 4, p = .29
I	1 (4)	4 (5)	
II	5 (18)	18 (24)	
III	10 (36)	15 (20)	
IV	6 (21)	28 (37)	
V	6 (21)	10 (13)	
Age at onset of major depressive disorder, mean (SD), y	28 (11)	30 (12)	t = 0.85, df = 101, p = .40
Family psychiatric history,[d] N (%)			χ^2 = 0.29, df = 1, p = .59
Positive	16 (57)	46 (63)	
Negative	12 (43)	27 (37)	
Comorbid nonpsychiatric medical illness, N (%)			χ^2 = 0.37, df = 1, p = .54
Yes	19 (68)	46 (61)	
No	9 (32)	29 (39)	

[a]Percentages do not always add to 100 because of rounding.
[b]Based on Satterthwaite's approximation.[26]
[c]Hollingshead-Redlich scale; I = highest socioeconomic status, V = lowest socioeconomic status.
[d]Data are missing for 2 subjects without tachyphylaxis.

which showed that the age at the beginning of the maintenance treatment intervals for the 2 groups was not significantly different (Z = 0.30, p = .76).

Survival analysis was used to calculate the time to recovery for the episodes of major depressive disorder that immediately preceded the 171 maintenance treatment intervals. There were 43 maintenance treatment intervals that resulted in tachyphylaxis; the median time to recovery for the depressive episodes that immediately preceded these 43 maintenance treatment intervals was 26 weeks. There were 128 maintenance treatment intervals that did not result in tachyphylaxis; the median time to recovery for the depressive episodes that immediately preceded these 128 maintenance treatment intervals was 27 weeks.

The sample included 34 subjects with multiple maintenance treatment intervals, i.e., subjects who were successfully treated for 2 or more episodes of major depressive disorder with an antidepressant and received maintenance pharmacotherapy after recovering from each episode. These subjects were thus at risk for multiple episodes of tachyphylaxis. Within this group of 34 subjects, the occurrence of tachyphylaxis during one maintenance treatment interval was not significantly associated with tachyphylaxis during the next maintenance treatment interval (κ = 0.01, p = .94).

Three preliminary mixed-effects logistic regression analyses examined the association of other clinical variables with tachyphylaxis. The first mixed-effects logistic regression examined the association of tachyphylaxis with clinical features of the episode of major depressive disorder that immediately preceded the maintenance treatment interval. These variables included severity of the episode (defined as the percentage of weeks during the episode for which the subject met the full criteria for major depressive disorder [PSR of 5 or 6, see Method]) (odds ratio [OR] = 2.21, 95% confidence interval [CI] = 0.96 to 5.07, Z = 1.87, p < .07), duration of the episode (OR = 1.01, 95% CI = 0.74 to 1.38, Z = 0.06, p = .96), melancholic subtype of major depressive disorder (RDC endogenous major depressive disorder) (OR = 2.58, 95% CI = 1.19 to 5.60, Z = 2.40, p < .02), and psychotic subtype of major depressive disorder (OR = 0.44, 95% CI = 0.02 to 11.09, Z = –0.50, p = .62).

A second preliminary mixed-effects model examined the association of lifetime course of illness with tachyphylaxis. These variables included number of lifetime episodes of major depression (OR = 0.92, 95% CI = 0.69 to 1.23, Z = –0.56, p = .58), lifetime history of comorbid alcohol dependence (OR = 0.58, 95% CI = 0.21 to 1.59, Z = –1.06, p = .29), lifetime history of comorbid anxiety disorder (RDC generalized anxiety disorder, panic disorder, phobic disorder, or obsessive-compulsive disorder) (OR = 1.19, 95% CI = 0.46 to 3.06, Z = 0.36, p = .72), and lifetime history of comorbid dysthymia (RDC chronic minor depressive disorder or intermittent depressive disorder for greater than 2 years) (OR = 1.94, 95% CI = 0.72 to 5.21, Z = 1.31, p = .19).

A third preliminary mixed-effects model examined the association of tachyphylaxis with clinical aspects of the maintenance treatment interval. These variables included duration of the maintenance treatment interval (OR = 1.003, 95% CI = 0.998 to 1.009, Z = 1.19, p = .24)

and the proportion of weeks with residual symptoms (1 or 2 symptoms at a mild level of severity with no impairment of functioning [PSR of 2, see Method]) during the 8-week recovery period and the subsequent maintenance treatment interval (OR = 1.67, 95% CI = 0.74 to 3.73, Z =1.24, p = .21).

The 3 preliminary mixed-effects models yielded 2 independent variables with $p < .10$: melancholic subtype of major depression (RDC endogenous major depressive disorder) immediately preceding the maintenance treatment interval and severity of the episode (defined as the percentage of weeks during the episode for which the subject met the full criteria for major depression [PSR of 5 or 6, see Method]). These 2 variables were then entered into a single reduced mixed-effects logistic regression model. In this model, the probability of tachyphylaxis was significantly increased more than 2-fold following recovery from an episode of melancholic major depression (OR = 2.52, 95% CI = 1.17 to 5.45, Z = 2.35, $p < .02$).

DISCUSSION

These results show that recurrence of major depression despite maintenance pharmacotherapy—tachyphylaxis—may be a common problem, occurring in approximately 1 of every 4 patients receiving maintenance treatment. This rate is very similar to the findings from the 3-year maintenance trial by Frank et al.[4] In their study, 21% of subjects randomly assigned to maintenance treatment with imipramine had a recurrence of major depression, and 24% of subjects randomly assigned to maintenance treatment with imipramine plus interpersonal psychotherapy had a recurrence.

Tachyphylaxis was twice as likely to occur in subjects with melancholic major depression prior to the maintenance treatment interval, compared to those with nonmelancholic major depression. The melancholic subtype of major depression may serve as a proxy for severity of illness, as melancholia occurs more frequently in severe episodes and in inpatients[27] and is associated with higher rates of suicidality.[28]

One issue that arises in the context of tachyphylaxis is whether the initial recovery from the episode of major depression was due to a "true," specific medication effect, which is thought to occur with delayed onset and which is subsequently persistent.[29] In contrast, a nonspecific placebo effect is thought to occur with early onset and to not persist. Tachyphylaxis in some situations may thus represent the lack of persistence that occurs in a nonspecific placebo response to medication. In the present study, recovery was defined as at least 8 consecutive weeks of euthymia, which is consistent with a persistent, specific medication effect. Additionally, the median time to recovery of 26 to 27 weeks is consistent with the delayed onset of a specific medication effect.

There are many limitations of the present study. One involves the CAD scores, which represent broad classes of treatment intensity that are somewhat coarse. The scale used to generate the CAD scores is based on the consensus judgment of the CDS investigators, owing to the lack of controlled data comparing graduated doses of antidepressants. Although the scale includes all medications approved by the U.S. Food and Drug Administration for treatment of major depressive disorder, cases treated with newer medications are probably underrepresented, because the most recently approved antidepressants have been available for the shortest time. It is not at all clear how readily one can extrapolate from the findings for tricyclics and monoamine oxidase inhibitors to selective serotonin reuptake inhibitors and other newer antidepressants. Furthermore, the CAD scale does not include information about side effects of antidepressants.

A further limitation of the present study is that the data are based on subject self-report. Plasma antidepressant levels were not monitored, nor were pills counted. Thus, the recurrent episodes of major depression that were observed during maintenance treatment may be due to noncompliance with treatment, rather than tachyphylaxis. An additional limitation is that the study did not examine maintenance psychotherapy, which can be efficacious in helping patients avoid recurrences of major depression.[4,7]

Another limitation is that the definition of tachyphylaxis was restricted to reappearance of major depression at full criteria. The nature of the dataset did not permit analyses examining the reappearance of moderate-to-marked symptoms less than those meeting the full criteria for major depression. Yet another limitation pertains to generalizability of the study sample. There are no minorities in the sample, and all subjects were initially recruited into the CDS at academic medical centers while seeking treatment, primarily as inpatients.

In considering the design of the present study, a randomized controlled trial may be superior in some regards. However, the trade-off is that observational data often include a wider range of subjects and psychopathology. As an observational study, the results from the present analyses are generalizable to an array of patients not necessarily eligible for randomized controlled trials.

The definition of maintenance pharmacotherapy in this study—a CAD score ≥ 3 (see Table 1)—was relatively robust. A prior study from the CDS found that subjects usually received much smaller doses of maintenance antidepressant medication after recovering from an episode of major depression and that 33% to 50% received no maintenance pharmacotherapy.[1]

An argument can be made that the term *tachyphylaxis* promotes a false dichotomy, in that maintenance treatment either works perfectly in eliminating all recurrences or does not work at all, as evidenced by at least 1 recurrence. This thinking has been conditioned by study de-

signs in which a recurrence marks the end of the study's maintenance phase. Clinicians, however, are not likely to discontinue a previously effective antidepressant as soon as the patient develops 2 weeks of a major depressive syndrome, unless the syndrome is relatively severe. Many patients may experience a number of mild recurrences, but over time, it becomes apparent that their course of illness on a given medication is more favorable than it had been without the medication. The results presented here largely avoid this fallacy because they incorporate multiple recurrences within individual subjects.

A recent review has addressed the possible mechanisms by which long-term treatment with antidepressants may lose its effectiveness or even adversely affect the course of depression.[30] It should be noted that within psychiatry, tachyphylaxis is not unique to major depressive disorder. In bipolar disorder, for example, lack of continued prophylaxis with lithium has been reported.[31]

In managing tachyphylaxis, increasing the dose of antidepressant medication[32] or adding cognitive behavior therapy[33] may be beneficial. Further research may show that tachyphylaxis occurs despite the best of maintenance treatment, including optimal pharmacotherapy and psychotherapy. Such findings would provide even more impetus to devote greater efforts to other interventions, such as primary prevention.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lithium (Lithobid, Eskalith, and others), nefazodone (Serzone and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil and others), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), venlafaxine (Effexor).

Study participants: The present study was conducted with the participation of the current CDS investigators: M. B. Keller, M.D. (Chairperson, Providence); W. Coryell, M.D. (Cochairperson, Iowa City); D. A. Solomon, M.D. (Providence); W. A. Scheftner, M.D. (Chicago); W. Coryell, M.D. (Iowa City); J. Endicott, Ph.D.; A. C. Leon, Ph.D.; J. Loth, M.S.W. (New York); J. Rice, Ph.D. (St. Louis). Other contributors include: H. S. Akiskal, M.D.; J. Fawcett, M.D.; L. L. Judd, M.D.; P. W. Lavori, Ph.D.; J. D. Maser, Ph.D.; T. I. Mueller, M.D.

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