Applicability of Clinical Pharmacotherapy Guidelines for Major Depression in Primary Care Settings

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Objective: To determine whether guidelines established for pharmacologic treatment of major depression are feasible in primary care.

Design: Prospective cohort study.

Setting: Ambulatory family health centers and internal medicine clinics.

Patients: Ninety-one primary care patients meeting criteria within the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* for a current major depression randomized to receive antidepressant medication after being judged by a psychiatrist as clinically eligible for pharmacotherapy in an ambulatory setting.

Intervention: Nortriptyline hydrochloride prescribed by primary care physicians trained in clinical guidelines specifying dosage schedules, durations, and procedures resembling those recommended by the AHCPR (Agency for Health Care Policy and Research) Depression Guideline Panel.

Main Outcome Measures: Patient participation and continuation in medication treatment.

Results: Fifty-five percent of patients completed the acute phase of treatment after a mean of 6.9 visits extending over a mean of 8.1 weeks. Of those patients entering the continuation phase, 60% completed the follow-up visits for 6 months. Taken together, only 33% of patients assigned to receive antidepressant medication completed the full regimen recommended by the AHCPR guidelines.

Conclusions: The treatment of depressed primary care patients within AHCPR guidelines for antidepressant medication is feasible but complex. Although primary care physicians ably adhere to these guidelines, keeping patients in treatment is difficult and possibly requires greater flexibility in treatment regimens.

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GROWING pressures to contain health care costs, reduce practice variations, and improve outcomes have led to the development of clinical guidelines defined by the Institute of Medicine as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[1] Among the guidelines that should help primary care physicians are those dealing with major depression, a disorder whose prevalence in ambulatory medical settings approximates 6% to 8%,[2] and for which early recognition and treatment can reduce unnecessary disability and even mortality.[3,4] Concern with how best to assess and treat episodes of major depression has led the Agency for Health Care Policy and Research (AHCPR) of the US Public Health Service[5] to establish guidelines for generalist physicians. Given the broad scope of its analytic efforts and the widespread dissemination of its recommendations, the reports by the AHCPR Depression Guideline Panel[6,7] constitute a clinical yardstick against which the practices of family physicians and internists may well be measured.[8]

The AHCPR guidelines that are most relevant to generalist physicians are those describing the use of medication to treat depression. These guidelines specify clinical indications as well as contraindications for antidepressant pharmacotherapy, frequency of office visits, medication dosage adjustments, use of drug blood levels, and procedures to follow in case of clinical nonresponse or relapse. Moreover, the AHCPR guide-

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PATIENTS AND METHODS

DESIGN AND SAMPLE SELECTION

The prospective cohort study reported here is part of a randomized control trial of treatments for major depression conducted in Pittsburgh, Pa, at four ambulatory facilities that serve largely lower socioeconomic class urban populations and that are affiliated with family practice or internal medicine residency training programs. Potential subjects were patients aged 18 to 65 years who presented in the waiting rooms at these sites, were not being treated for depression, and were not pregnant. The patients were assessed through a multiphase evaluation to identify those meeting diagnostic and severity criteria for major depression and to exclude those with comorbid medical and/or psychiatric illness (**Table 1**) that would contraindicate randomization to one of the study's three treatment cells, ie, interpersonal psychotherapy, nortriptyline hydrochloride pharmacotherapy, and a physician's usual care. Depressed patients with contraindications to treatment in the outpatient medical setting, such as serious suicidality, were also excluded.

The evaluation process began with a research associate approaching patients in the health center waiting room and informing them that we were studying treatments for depression in a protocol approved by the University of Pittsburgh Biomedical Institutional Review Board. Patients providing informed consent were screened with the Center for Epidemiologic Studies-Depression (CES-D) Scale.[14] This 20-item instrument measures mood and neurovegetative symptoms during the preceding week, with possible scores ranging from 0 to 60. Patients scoring 22 or higher on the CES-D Scale were administered the "Depression" section of the Diagnostic Interview Schedule (DIS),[15] a highly structured instrument that has been modified[16] to formulate current as well as lifetime psychiatric diagnoses within the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*.[17]

Patients who were judged by the modified DIS to meet criteria for a current major depression were interviewed by a consultation-liaison psychiatrist who also reviewed the patient's medical chart and ordered laboratory tests as needed. The purposes of this third assessment phase were to (1) ascertain that the patient was experiencing a major depression of sufficient, yet not undue, severity warranting treatment that could be provided safely in an ambulatory medical setting and (2) ensure that the patient was not experiencing comorbid psychiatric or medical illness precluding a randomized treatment assignment to any of the three treatment conditions. For example, the psychiatrist excluded patients with organic mood syndromes such as those caused by endocrine problems or medications, but not depression possibly reactive to a medical condition or disability.

PHARMACOTHERAPY PROTOCOL

The study was designed in 1989, at which time we considered nortriptyline the best antidepressant medication for medical patients because (1) its efficacy and therapeutic dosage range had been demonstrated with psychiatric patients[7]; (2) it achieves therapeutic effects at lower dosage levels than other tricyclics; and (3) it is less likely to produce toxic side effects such as orthostatic hypotension in a population already at risk for untoward medical complications.[18] Given our aim of testing the feasibility and effectiveness of treatments for depression in routine primary care practice,[13] patients were treated in their usual ambulatory care site but at no cost for visits or the medication. Pharmacotherapists were residency-trained family practitioners or general internists who were provided didactic education in protocol procedures by the study's family practitioner coprincipal investigator (M.R.B.) through a written manual adapted from prior such manuals[19,20] for use in primary care practice. They also were required to demonstrate clinical proficiency by successfully completing the treatment of two nonstudy patients who met protocol criteria. During the study, visits between the patient and the physician were audiotaped and concurrently monitored to ensure that each treatment phase was rendered as specified by the study's protocol. The acute phase aimed for improvement in the patient's clinical status, the continuation phase aimed for stability of the improvement, and the termination phase sought to prevent relapse.

Patients met with the pharmacotherapist to whom they were assigned as soon as possible after completing the assessment. Patients were seen in their usual health care setting within routine procedures, ie, they were greeted by a nurse who obtained weight and vital signs, including orthostatic blood pressure readings under standard conditions. Patients were then seen by the pharmacotherapist who reviewed the patient's medical and psychiatric history and determined that there was no orthostatic hypotension at baseline. If any contraindications to nortriptyline therapy were detected, treatment was not initiated. Patients were educated about their depression, expected side effects of the medication, and expected time course to improvement. The clinicians were taught to be focused on depressive symptoms and to model their treatment of depression after that of other illnesses such as hypertension.

To avoid contamination of the psychotherapy arm of the randomized control trial,[13] physicians avoided discussion of psychosocial problem areas. When patients introduced such problems, they were acknowledged, but exploration was not encouraged. As with any medical illness, clinicians were permitted to gather information; to get to know the patient personally; to convey concern about the illness; and to display warmth, empathy, and support. Clinicians also were encouraged to promote a therapeutic alliance with the patient by offering reassurance and information so as to maximize treatment compliance and relieve anxiety.

During the acute-treatment phase, patients met with pharmacotherapists weekly or biweekly as the initial nortriptyline hydrochloride dose of 25 mg was increased in 25-mg increments to a therapeutic dosage as determined through blood levels and symptoms checked at each visit. Nortriptyline's usual target level of 190 to 570 nmol/L (50 to 150 ng/mL) was narrowed when possible to 304 to 456 nmol/L (80 to 120 ng/mL) to provide an additional margin of safety given that medical patients often have illnesses or are prescribed other drugs that may alter nortriptyline levels. At the initial session, which lasted 45 to 60 minutes, the clinician assessed suicidal ideation, intent, or impulses, and addressed any resistance to the an-

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tidepressant medication. Potential side effects of the nortriptyline were sought at this and subsequent visits, and were rated on the Side Effects Scale.[21] Patients were informed that nortriptyline is not addicting, that it has a specific effect on a chemical imbalance, that most but not all patients respond, and that other drugs such as tranquilizers and alcohol should be avoided. Most important, the clinician and patient together agreed on the patient's most troubling "target" symptoms for regular monitoring to determine whether the depression was remitting.

Subsequent sessions were typically completed within 12 to 15 minutes to (1) avoid contaminating the other study cells, (2) maintain treatment parity across patients and clinicians, and (3) coincide with the duration of most patient visits in primary care practice. These follow-up visits were devoted primarily to a review of the patient's target symptoms and side effects. The patient was asked specifically to comment on symptoms and the medication. A typical session might begin, "So how are you feeling on the medicine?" Weight, vital signs, and orthostatic blood pressures were recorded and a blood sample was obtained to determine the nortriptyline blood level. If patients described symptoms unrelated to the depression or its treatment, they were referred to their regular primary care physician. Potential side effect symptoms were specifically sought at each visit. Patients were seen weekly while the dose of nortriptyline was increased to a therapeutic level and symptoms abated. Once a stable dose was achieved, clinicians had the discretion, similar to that in everyday practice, of seeing patients weekly or biweekly until they were thought to be clinically improved. The goal was for patients to improve within 6 to 8 weeks.

The acute phase of treatment was considered complete when the patient was assessed as having reached a "point of stability." The criteria for this determination typically were that (1) their patients had clinically improved as reflected in their reports about symptoms, (2) the nortriptyline blood level was within the 190- to 570-nmol/L (50- to 150-ng/mL) therapeutic window on three consecutive tests, (3) the physician considered monthly visits sufficient, and (4) we were aware that the patient's Beck Depression Inventory (BDI) score was markedly improved over that at the start of treatment. If the patient's symptoms failed to improve within approximately 6 weeks and a psychiatrist consultant judged the patient to be a nonresponder to nortriptyline, the patient was referred back to his or her primary care physician within the health center for alternative treatments outside of the study protocol.

Patients successfully completing the acute phase of treatment continued receiving the same dosage of nortriptyline at which they had achieved a steady therapeutic blood level, and they were then seen for continuation-phase visits for 6 months. As during the acute phase, patients whose depression relapsed were referred back to their primary care physician for assessment and treatment within standard health center procedures. Patients remaining well throughout the 6-month continuation phase had their medication tapered over several weeks and were instructed possibly to expect symptoms of cholinergic rebound such as lethargy and nausea. Continuation-phase pharmacotherapy was terminated when the nortriptyline was successfully tapered. In the 25% of instances in which patients asked or were advised to continue taking the medication beyond the 6 months, treatment was continued by the patient's primary care physician within the health center.

DATA ANALYSIS

In addition to calculating the frequencies with which patients participated in the acute and continuation phases, we sought to identify variables related to completion of the acute phase. The clinical variables selected for this analysis were baseline severity of the depression as measured by scores on the CES-D, the Hamilton Rating Scale-Depression, and the BDI; health status as measured by the Duke Severity of Illness Scale, the Health Locus of Control Scale, and the Side Effects Scale; physical, social, and emotional functioning as measured by the Medical Outcomes Study Short Form-36 and the Global Assessment Scale; social support as measured by the Interpersonal Support Evaluation List; stressful life events as measured by the Psychiatric Epidemiology Research Interview; and use of mental health services during the preceding 3 months and lifetime as reported by the patients.

lines describe specific procedures for the acute, continuation, and maintenance phases of pharmacotherapy.

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Despite the evident merit of the recommendations by the AHCPR Depression Guideline Panel, they are predominantly based on studies conducted in psychiatric tertiary care centers.[7] The validity of generalizing these clinical standards and procedures to routine primary care practice is unknown. Physicians in primary and tertiary care centers differ in their interests and skills, and the cause, manifestations, severity, and course of major depression in medical and psychiatric patients likely differ as well.[9] Furthermore, there are few reports of whether depressed primary care patients will participate in and comply with the recommended guidelines, ie, will they make frequent office visits during the acute phase of treatment, take increasingly higher dosages of the drug, permit blood levels to be monitored, and return for follow-up once they are feeling better? In one of the few studies relevant to these concerns, Katon et al[10] found that only 34% of distressed high utilizers of health maintenance organization services filled four or more prescriptions for newer-generation antidepressant medications during a 6-month period. In a related study at the same health maintenance organization facility, Simon et al[11] similarly found high rates of drug discontinuation by the center's medical patients and apparently inadequate dosages prescribed by their primary care physicians.

A unique opportunity to investigate whether guidelines established for pharmacologic treatment of depression are feasible in primary care is afforded by our randomized control trial funded by the National Institute of Mental Health.[12,13] The trial compares the effectiveness of pharmacotherapy, psychotherapy, and a physi-

Table 1. Pharmacotherapy Exclusionary Criteria

Psychotic features associated with the major depression
Suicidal ideation, plans, and prior attempts precluding treatment in primary care practice
History of bipolar illness
Organic mood syndromes, including those secondary to medical illness or drugs
Medical contraindications to nortriptyline hydrochloride: (1) known nortriptyline hydrochloride hypersensitivity; (2) pregnancy; (3) myocardial infarction within 1 month; (4) first- (PR interval on electrocardiogram greater than 0.18), second-, or third-degree heart block; (5) malignant ventricular arrhythmias; (6) urinary retention; and (7) acute narrow-angle glaucoma
Unstable medical condition as indicated by clinical history, physical examination, and/or laboratory findings
Alcohol or other substance abuse disorder within past 2 months

Table 2. Demographic and Baseline Clinical Characteristics of Sample Patients (N=91)*

Median age, y	38.0
Race, % W	59.3
Sex, % F	80.2
Marital status, % m	35.2
Education level, % high school or more	79.1
Employment status, % unemployed	55.6
Mean CES-D	37.3
Mean BDI	25.5
Mean HRS-D	23.7
% Other lifetime psychiatric disorder (Axis I)	75.3
% Any lifetime personality disorder (Axis II)	64.2

**CES-D indicates Center for Epidemiologic Studies-Depression; BDI, Beck Depression Inventory; and HRS-D, Hamilton Rating Scale-Depression.*

cian's "usual care" in treating medical outpatients who are experiencing a major depression. This article describes one arm of the study in which pharmacotherapy is provided by primary care physicians within a protocol closely resembling the AHCPR guidelines[7] and reviews treatment histories of 91 patients randomized to receive an antidepressant medication. Data are presented about patient compliance with treatment procedures during the acute and continuation phases, and factors associated with attrition during each of these intervention periods are analyzed. Data collection regarding the clinical course of the depression and the patient's subsequent mental and physical functioning continues, and they will be reported in a subsequent analysis.

RESULTS

From March 1991 through December 1993, a total of 9938 patients were asked to participate in the study's three sequential assessments. Of this group, 7652 (77%) completed the CES-D screening instrument; of this number, 1913 (25%) scored above the cutoff score of 22 used in this study. The "Depression" section of the DIS was then administered to the 1059 patients not presently being treated for a mood disorder and consenting to this second assessment. Among this group, the DIS identified 678 (64%) patients as experiencing a current major depression, and they were referred to a psychiatrist for a clinical interview. Only 403 (59%) completed this third assessment phase, of whom 283 (70%) were judged by psychiatrists as experiencing a major depression treatable in a primary care setting.[13,22] Informed consent for a randomized treatment assignment was provided by 276 (98%) of the protocol-eligible patients.

Demographic and clinical characteristics of the 91 such patients assigned to pharmacotherapy on the basis of an a priori power calculation[12] are presented in **Table 2**. The group was middle-aged, divided between whites and nonwhites, and predominantly female; only one third of its members were married, more than half were unemployed, and the vast majority had completed at least high school. The severity of depression experienced by these patients was quite high given that their mean baseline scores of 37.3 on the CES-D, 25.5 on the BDI, and 23.7 on the Hamilton Rating Scale-Depression significantly exceeds accepted cutoff scores on these instruments for probable depression (27 on the CES-D, 15 on the BDI, and 17 on the Hamilton Rating Scale-Depression). Furthermore, 75% of the group met lifetime criteria for another psychiatric disorder (Axis I) as measured by the DIS, and 64% met criteria for a personality disorder (Axis II) as measured by the Structured Clinical Interview for *DSM-III* Personality Disorders.

The 91 patients were assigned among 12 trained pharmacotherapists, who each treated a mean of 7.6 patients (range, 1 to 14). The median interval between randomization and the initial pharmacotherapy session for the 78 patients attending was 1.1 weeks (range, 0.3 to 8.0); 80% of the patients were seen within 2 weeks. Of those treated, 64% (50/78) achieved a clinical point of stability after a mean of 6.9 visits (range, 3 to 14) extending over a mean period of 8.1 weeks (range, 2 to 21). At the point of stability, patients who completed the acute-treatment phase were prescribed a mean daily dose of 103 mg nortriptyline and their mean blood level was 338 nmol/L (89 ng/mL). Fifty (55%) of the 91 patients assigned to receive medication completed the treatment's acute phase, but 41 (45%) did not (**Table 3**).

Owing to poor response, 11 (27%) of 41 patients dropped out of the study as directed by their physicians; ie, they resulted from the judgment by the primary care physician and consulting psychiatrist that the patient's major depression was not improving (even though blood levels were within the therapeutic window for six of the 11 patients). The other 30 patients (73%) dropped out on their own. Eleven of these latter dropouts visited the physician at least twice; only three had a therapeutic blood level when ceasing treatment. Blood level data were not obtainable for the 13 patients who did not keep any appointment and the six who appeared but once.

Among the 50 patients entering the continuation phase after achieving the point of stability, 20 (40%) failed to complete the six monthly visits required in this second segment of treatment (Table 3). Four (20%) of the 20 dropouts resulted from physician concern about a patient's deteriorating clinical state and one patient dropped out because of pregnancy. The

Table 3. Treatment History of Patients Completing Nortriptyline Pharmacotherapy

	No. (%) of Patients
Acute Phase	
Treatment completed	50 (54.9)
Dropout	41 (45.1)
Total	**91 (100.0)**
Continuation Phase	
Treatment completed	30 (60.0)
Dropout	20 (40.0)
Total	**50 (100.0)**

Table 4. BDI Scores: Acute-Phase Dropouts*

	No. of Patients	First Session	Point of Dropout
Initiated by patient			
0 session	13	NA	NA
1 session	6	26.3 (11.9)	NA
≥2 sessions	11	29.0 (10.4)	21.4 (11.6)
Initiated by physician	11	35.3 (11.9)	31.9 (13.7)

**Data are reported as mean (±SD). BDI indicates Beck Depression Inventory; NA, not applicable.*

Table 5. BDI Scores: Continuation-Phase Dropouts*

	No. of Patients	Baseline	Point of Stability	Point of Dropout
Initiated by patient	15	27.7 (9.1)	7.5 (5.6)	7.2 (8.3)
Initiated by physician	5	29.2 (15.2)	17.8 (17.0)	17.4 (13.2)

**Data are reported as mean (±SD). BDI indicates Beck Depression Inventory.*

other 15 (75%) dropouts were patient initiated. Conversely, 60% (30/50) of the patients completed the protocol's requirement of continuing the medication and making at least six monthly visits to the physician. Taken together, the data in Table 3 indicate that only 33% (30/91) of patients randomized to pharmacotherapy participated in the full treatment regimen that AHCPR guidelines[7] deem necessary to achieve remission and forestall a relapse.

Given this finding, we analyzed demographic and clinical variables that might explain this population's high rate of premature termination. The six demographic characteristics (Table 2) failed to distinguish the two groups. Comparisons of the patients who did and did not complete the acute phase on the 13 clinical variables specified in the preceding "Data Analysis" subsection in the "Patients and Methods" section found the groups to differ significantly on initial measures of depressive severity, global functioning, perception of control over health status, and recent visits to a mental health specialist. When compared with patients who completed the acute-treatment phase, those dropping out prematurely (1) were more depressed as assessed by self-report on the CES-D (P=.05) and the BDI (P=.005), as well as by clinician ratings on the Hamilton Rating Scale-Depression (P=.056); and (2) functioned more poorly as assessed by blind evaluators on the Global Assessment Scale (P=.02). In addition, dropouts described themselves on the Health Locus of Control Scale as having less control of their health than patients who completed treatment (P=.05), and 22% of them had visited a mental health specialist in the 3 months preceding randomization vs only 2% of those remaining in treatment (P=.004).

Our finding that more severe depression is related to briefer participation in treatment led us to compare BDI scores at the initial session and at the point of dropout for patients who chose to terminate prematurely (**Table 4**). Applying the convention of Frank et al[23] for classifying the severity of BDI scores, we found that 81% of patients fully symptomatic at baseline and dropping out prematurely remained fully symptomatic when deciding to leave treatment. The opposite pattern applies to patients choosing to drop out of the continuation phase before completing its required six monthly follow-up visits (**Table 5**). In this subgroup, further analyses of the data in Table 5 indicate that at the point of dropout, 74% were asymptomatic, 13% were partially symptomatic, and 13% were fully symptomatic.

COMMENT

Despite Roper[24] poll findings about the great reluctance of most Americans to take a medication for relief of depression, primary care physicians commonly prescribe antidepressant drugs for this disorder.[25,26] The high volume of such prescriptions and the need for adequate dosage and treatment duration led the AHCPR Depression Guideline Panel[7] to formulate guidelines that it deemed applicable to primary care practice. However, the resulting recommendations are based on findings from psychiatric clinical trials that typically fail to consider patient factors, treatment environment, and provider characteristics as well as drug interactions specific to the primary care setting. Such concerns about transferring complex therapeutic regimens across patient populations and practice settings led Kupfer and Freedman[27] and Keller and Lavori[28] to urge that researchers design treatment effectiveness studies more closely approximating the tasks facing clinicians in routine daily practice.

Accepting this challenge, our study incorporated features that intended to balance generalizability and scientific rigor.[13] Thus, depressed patients randomized to pharmacotherapy were treated by primary care physicians, the treatment was provided directly within the health center, and the nortriptyline hydrochloride was prescribed in dosages and for durations closely resembling those recommended by the AHCPR Depression Guideline Panel.[7] In addition, most of the study patients at baseline exhibited the severe levels of depression (Table 2) known to benefit from medication.[29] Given this methodologic effort to balance external and internal validity considerations, what do our data suggest about the feasibility of applying guidelines successful in psychiatric settings to the treatment of major depression in routine primary care practice?

More than half of the patients (55%) randomized to the medication followed the protocol and improved (Table 3). This finding indicates that primary care physicians can apply treatment procedures within AHCPR standards and have the majority of patients comply to the point of achieving what physicians judge to be clinical improvement. However, 45% of the patients did not achieve a point of stability, either because they dropped out or did not improve.

How is patient noncompliance to be understood given that (1) pharmacotherapists made persistent efforts through telephone calls and letters to encourage patients to resume treatment and (2) patients were not charged for the visits or for the nortriptyline? Interviews with patients who dropped out suggest that this may be attributable in part to our research design wherein some patients did not wish to take the medication despite agreeing to a randomized treatment assignment. Furthermore, those accepting it were treated by an unfamiliar primary care physician who focused on depressive symptoms and minimized discussion of psychosocial problems. Conceivably, discussion of such problems are part of the clinical treatment typical of routine practice that could have reduced attrition.

Noncompliance could also have been related to patient intolerance of physical symptoms correctly or incorrectly attributed to the drug. However, our finding that patients who were prescribed nortriptyline had high pretreatment scores on the Side Effects Scale,[21] which typically *decreased* after starting the drug, suggests significant somatization in this group. Physicians, thus, should carefully elicit such symptoms among their patients before prescribing an antidepressant medication so as to minimize inaccurate attribution of physical symptoms of depression or a comorbid organic disorder to the drug.[30] The need for such an assessment also would apply when physicians prescribe selective serotonin reuptake inhibitor antidepressant medications, from which there appears to be lower attrition caused by side effects than from first- and second-generation antidepressant medications.[10,31]

In addition to these possible reasons for noncompliance, patient self-reports and clinician ratings suggest that severe depressive illness at baseline, despite recent contacts with a mental health professional, reduces the patient's adherence to treatment recommendations. This finding raises the questions of whether primary care patients presenting with higher depressive severity require different treatment from that offered in our protocol, eg, pharmacotherapy combined with psychotherapy, or referral to a mental health professional specializing in the care of complex mood disorders.

Finally, a subgroup of particular interest with regard to compliance are the 13 patients (14% of the total sample) who, despite agreeing to a randomized treatment assignment, failed to appear even for the initial pharmacotherapy visit. These medication "no shows" often had expressed a preference for the psychotherapy assignment when providing informed consent, and presumably were disappointed at failing to get it. This subgroup, thus, possibly resembles the many patients in routine primary care practice who refuse medication, who accept a prescription and do not fill it, or who accept a referral but make no appointment with the specialist. These behaviors reinforce the AHCPR Depression Guideline Panel's[7] emphasis on the vital need to consider patient preference when selecting a depression-specific treatment.

Primary care physicians must be knowledgeable not only about the dosage and duration requirements of antidepressant treatment but also about the need for continuing medication for approximately 6 months to consolidate clinical response and prevent relapse. As physicians become increasingly aware of the AHCPR Depression Guidelines and prescribe antidepressant medications for an extended period, what response may be anticipated from their patients? Our data suggest that in routine practice, the majority will adhere to extended treatment, but a significant minority will not. In our study, the continuation-phase dropouts typically were feeling well and possibly believed that they no longer needed medication. (Subsequent analyses of patients who completed treatment and intent to treat types will clarify the value of continuation treatment among primary care patients.)

The compliance problem encountered with depressed patients resembles that which vexes primary care physicians treating patients for hypertension, 50% of whom similarly fail to keep follow-up appointments and 40% of whom fail to take their medications as prescribed.[32] Controlled trials of physician and patient educational interventions have long been recognized as needed to clarify strategies capable of increasing patient adherence to antihypertensive treatment.[33] We reiterate the call by Katon et al[10] for similar research on strategies for improving patient compliance with antidepressant medications.

In summary, our data support the feasibility of practicing "guideline pharmacotherapy" with a sizable proportion of depressed primary care patients. However, our study emphasizes the difficulties in doing so. Patient adherence to medication must be enhanced, possibly through discussion of psychosocial problems and/or by offering alternative psychological therapies and antidepression medications when clinically appropriate and feasible. Such strategies and others are equally crucial once patients are asymptomatic, as they are then prone to end treatment prematurely.

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Conversions From Système International (SI) Units to Traditional Units (Modified From *The SI Manual in Health Care*)

System	Component	SI Reference Interval*	SI Unit	Conversion Factor (Divide by)	Traditional Reference Interval*	Traditional Unit
Plasma	Nortriptyline, therapeutic	90-760	nmol/L	3.797	25-200	ng/mL

**These reference values are not intended to be definitive since each laboratory determines its own values. They are provided for illustration only.*