Symptoms of Major Depression and Tricyclic Side Effects in Primary Care Patients

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OBJECTIVE: To examine the prevalence and course of symptoms resembling side effects of tricyclic antidepressants among primary care patients experiencing major depression and receiving nortriptyline pharmacotherapy.

DESIGN: Prospective cohort study.

PATIENTS: Seventy-five patients meeting DSM-III-R criteria for a current major depression.

SETTING: Four Pittsburgh (Pa.) ambulatory health centers affiliated with residency programs.

MEASUREMENTS AND MAIN RESULTS: Symptoms resembling tricyclic side effects were assessed at baseline and at monthly intervals using the Somatic Symptoms Checklist. The Hamilton Rating Scale for Depression and Diagnostic Interview Schedule were used to assess depressive severity and history of generalized anxiety or panic disorder, respectively. Symptoms resembling tricyclic side effects, including thirst (54%), palpitations (51%), and dry mouth (48%), were commonly experienced before commencing pharmacotherapy. Patients with severe depressive episodes and those with a history of an anxiety or panic disorder had significantly more physical symptoms than those with milder episodes of depression and were more likely to drop out of care ($n = 25$) before completing the acute phase of pharmacotherapy. Patients who completed the acute phase of pharmacotherapy and those who entered its continuation phase ($n = 43$) experienced significant reductions in many depressive and physical symptoms ($p < .001$).

CONCLUSIONS: Symptoms resembling tricyclic side effects are common among depressed primary care patients before beginning pharmacotherapy and generally remit with the depressive episode. Better awareness of major depression's somatic effects and the consequences of therapy could result in better management of both physicians' and patients' expectations regarding antidepressant pharmacotherapy.

KEY WORDS: major depression; primary care; pharmacotherapy; nortriptyline; adverse effects.

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Major depression is experienced by 6% to 8% of primary care patients,¹ and is associated with significant psychic distress and functional disability.²⁻⁵ A meta-analysis of randomized clinical trials by the Depression Guideline Panel of the Agency For Health Care Policy and Research concluded, however, that most episodes of this disorder can be resolved efficaciously when antidepressant medications are prescribed at proper dosages and for adequate durations.⁶ Thus, it is of concern that primary care physicians often prescribe these drugs at dosages too low to achieve therapeutic benefits and for periods too brief to prevent relapse.⁷⁻¹¹

The rationale guiding prescribing practices of primary care physicians has been the subject of much speculation. One possibility for why antidepressant medications, particularly of the tricyclic type, are prescribed at subtherapeutic dosages is that they produce disturbing side effects for patients who already are highly sensitive to the psychological and somatic symptoms associated with their depressive illness. Medication-induced discomforts such as thirst, dry mouth, palpitations, and dizziness, which are most marked early in the course of treatment, could lead the patient to terminate pharmacotherapy prematurely. When this occurs, remission from the episode is hindered and the probability of relapse increases. Presumably physicians prescribe antidepressants at quite low initial and continuing dosages so that discomforts are better tolerated and participation in treatment is sustained.¹² Still, the physician must consider whether the discomforting psychological and somatic symptoms attributed to the antidepressant medication are actually manifestations of the mood disorder itself.

Symptoms resembling the side effects of tricyclic antidepressants have been found among depressed psychiatric,¹³⁻¹⁵ geriatric,¹⁶ and primary care¹⁷⁻¹⁹ patients even before these medications were provided them. Given these earlier reports, more information is needed about the relation between subjective symptoms resembling tricyclic side effects and the severity of the depressive episode along with the influence of a comorbid anxiety disorder on these symptoms. It also remains unclear which preexisting psychological or physical depressive symptoms affect the primary care patient's adherence to a prescribed antidepressant medication and which particular symptoms remit with the passage of time while using them.

The opportunity to study these concerns arose in the course of our University of Pittsburgh Institutional Review Board-approved randomized clinical trial investigating the effectiveness of a standardized medication protocol in treating major depression among primary care patients.²⁰ Our analyses of preexisting symptom patterns and their clinical course could help primary care physicians better educate

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their patients about the properties of antidepressant medications, their side effects, and their impact on various depressive symptoms. Sharing this knowledge with patients may also enhance their adherence to prescribed drugs,²¹⁻²⁴ an aspect of antidepressant pharmacotherapy still requiring improvement in the primary care setting.⁷

METHODS

Patients

Primary care patients experiencing a current major depression were recruited for the treatment study at four Pittsburgh ambulatory health centers between 1991 and 1994. These centers serve a predominantly lower-socio-economic-class population, and are affiliated with either a family practice or an internal medicine residency training program.

All patients aged 18 to 65 years in the waiting rooms of the health centers were screened for major depression with the 20-item Center for Epidemiologic Studies—Depression (CES-D) scale.²⁵ Of the 7,652 patients completing the CES-D, 1,913 (25%) scored at or above the study's positivity criterion of 22. We excluded 421 of these high-scoring patients who were already being treated for a mood disorder. Of the remaining, 1,059 (71%) completed the Depression section of the Diagnostic Interview Schedule,²⁶ and 678 (64%) of these met DSM-III-R criteria for a current major depression. These patients were then referred to a consultation-liaison psychiatrist to be assessed for eligibility to participate in the clinical trial based on various inclusionary and exclusionary criteria.²⁷ No differences in clinical severity of the depressive episode as measured by the CES-D, past use of mental health services, or educational attainment were found between the 403 patients (59%) who presented for the evaluation and the 275 (41%) who did not. However, participants were significantly older (38 vs 33 years of age), less often female (81% vs 90%), and more likely to have visited a mental health specialist in the past (56% vs 43%).²⁷ The psychiatrists judged 283 (70%) of the 403 patients they evaluated as "protocol-eligible." These 283 individuals had a similar level of depressive severity as the 120 patients who scored positive on the Diagnostic Interview Schedule but were evaluated and found to be protocol-ineligible. Informed consent for a randomized treatment assignment was subsequently provided by 276 (98%) of 283 eligible patients.

Enrolled subjects were randomized to one of three interventions: antidepressant medication in the form of nortriptyline (NT) provided by board-certified family practitioners or internists trained in protocol pharmacotherapy,²⁸ interpersonal psychotherapy provided by psychiatrists or psychologists, or "usual care" provided by the patient's primary care physician. No significant differences in sociodemographic or clinical characteristics, including depressive severity, were uncovered among the 276 study subjects who were randomized to each of the

three study arms.²⁰ Of the 91 patients randomized to pharmacotherapy, 13 (14%) did not keep their initial appointment. The Somatic Symptoms Checklist (described below) was not administered at baseline to three of the remaining 78 patients. The subsequent analyses are based, therefore, on data gathered from 75 patients.

Clinical Assessments

The sociodemographic characteristics of protocol patients were determined before the start of treatment. Depressive severity was assessed at baseline as well as at monthly intervals during pharmacotherapy's acute phase with the Hamilton Rating Scale for Depression (HRS-D)²⁹ by trained clinical evaluators blinded to a subject's treatment assignment in the randomized control trial. Following the convention suggested by Elkin et al.,³⁰ HRS-D scores of 19 or below indicated mild-moderate depressive symptomatology and scores of 20 or greater indicated severe symptomatology. Patients also completed the Beck Depression Inventory³¹ at each pharmacotherapy visit with the primary care physician to provide the clinician and investigators another index of their depressive severity. Level of overall functioning was rated on the Global Assessment Scale,³² and degree of general medical comorbidity was rated on the Duke Severity of Illness Index.³³ Because anxiety disorders comorbid with major depression can intensify the presenting mood symptoms³⁴ and adversely affect the depression's clinical course,³⁵ we administered the general anxiety disorder and panic disorder sections of the Diagnostic Interview Schedule²⁶ at baseline to determine whether subjects met lifetime criteria for either of these conditions.

Side Effects of Tricyclic Antidepressants

The number and severity of complaints usually associated with the side effects of tricyclic antidepressants were assessed with the Somatic Symptoms Checklist.³⁶ Pharmacotherapists rated each patient on the checklist's 5 mood and 11 physical symptoms using 4-point Likert scales (0-3), which generated scores for each symptom category as well as a total symptom score. These scores were generated before the patient started the NT as well as at each follow-up visit to the pharmacotherapist.

Pharmacotherapy

Protocol subjects randomized to pharmacotherapy were prescribed NT at their health center by a primary care physician who had been trained in the standardized protocol for this treatment.³⁷ Patients initially met with the pharmacotherapist weekly and then biweekly as the initial 25 mg/day of NT was increased in 25-mg increments until achieving a stable NT serum level of 50 to 150 ng/mL on serial blood tests. Subjects were not charged

for the medication, serum NT drug level tests, or their visits with the pharmacotherapist.

For purposes of this study, the acute phase of pharmacotherapy was considered complete when the primary care physician and the investigator assessed a patient as having reached a "point of stability." The criteria for this clinical determination were intended to resemble those applied by primary care physicians in routine practice: i.e., (1) the patient's symptoms had improved; (2) the pharmacotherapist considered monthly follow-up visits sufficient; and (3) the NT blood level was in the range of 50 to 150 ng/mL on three consecutive visits.³⁷ Patients whose depressive symptoms failed to improve within 6 weeks and who continued to score at least 20 on the Beck Depression Inventory were assessed by a psychiatric consultant. Patients judged as medication nonresponders were referred back to their regular primary care physician for alternative treatments in accordance with standard health center practices ($n = 11$). Another 14 patients independently initiated the decision not to complete the acute phase of pharmacotherapy. Thus, 25 patients did not achieve a point of stability ("dropouts") while 50 patients did and were considered "completers" of the acute phase of treatment. Members of the latter group then entered into pharmacotherapy's continuation phase and scheduled for monthly visits with their pharmacotherapist.

Data Analysis

The frequency distributions of baseline sociodemographic, clinical, and psychiatric variables were examined and grouped in relation to the presence or absence of symptoms assessed by the Somatic Symptoms Checklist. Differences across groups and at successive time points were analyzed for statistical significance through repeated measures of analysis of variance (ANOVA). Values of $p \leq .05$ were considered to indicate statistical significance by a two-tailed test. Paired ANOVA tests were performed to further characterize intergroup differences when significant differences were detected across three successive time points (baseline, point of stability, and last continuation-phase visit). All statistical procedures were performed using the SPSS statistical software package.

RESULTS

The sociodemographic and clinical characteristics of the 75 patients randomized to pharmacotherapy for treatment of major depression and for whom baseline Somatic Symptom Checklist scores were available are presented in Table 1. The majority of the cohort was female, white, and had graduated from high school. Almost half of its members were employed, but only one third were married at the time of study entry. As for the group's clinical status, its depressive symptomatology as assessed by the HRS-D was severe, overall level of functioning as rated on the Global Assessment Scale poor to moderate, and degree of medi-

Table 1. Baseline Characteristics of Patients Experiencing a Current Major Depression ($n = 75$)

Characteristic	Mean Value (SD) or Percentage
Sociodemographic	
Age, mean years (SD)	39 (11.6)
Female, %	77
White, %	59
Married, %	35
Education $\geq$ high school, %	77
Employed, %	46
Clinical	
Hamilton Rating Scale, Depression (HRS-D), mean value (SD)	23.8 (5.3)
Global Assessment Scale, mean value (SD)	50.4 (7.7)
Duke Severity of Illness Index, mean value (SD)	34.6 (15.0)
Generalized anxiety disorder, lifetime, %*	41
Panic disorder, lifetime, %*	29

* $n = 68$.

cal burden as evaluated by the Duke Severity of Illness Index moderate. The complexity of psychiatric morbidity experienced by the cohort is evident in that more than two thirds of its members met diagnostic criteria for an earlier episode of generalized anxiety disorder or panic disorder.

Table 2. Frequency of Symptoms and Somatic Symptom Checklist Score Before Initiating Tricyclic Pharmacotherapy

Symptom	% Experiencing	Mean Symptom Score* (SD)
Depressive		
Fatigue	93	1.67 (0.70)
Agitation†	78	1.10 (0.73)
Headache	56	0.72 (0.75)
Confusion	53	0.71 (0.75)
Hallucinations†	4	0.04 (0.20)
Physical		
Thirst†	54	0.57 (0.55)
Palpitations	51	0.68 (0.74)
Dry mouth	48	0.55 (0.62)
Dizziness	44	0.51 (0.62)
Perspiration	41	0.44 (0.55)
Nausea	39	0.48 (0.67)
Tremor	36	0.41 (0.60)
Constipation	35	0.44 (0.66)
Blurred vision	35	0.36 (0.51)
Slurred speech	21	0.21 (0.41)
Urinary difficulty†	8	0.10 (0.34)

*0 = absent; 1 = elicited by inquiry; 2 = reported spontaneously; 3 = severe enough to require dosage change.

† $n = 74$.

Table 3. Relation of Severity of Hamilton Rating Scale for Depression (HRS-D) and Somatic Symptom Checklist Scores at Baseline

Symptom	Mean Symptom Score (SD)		p Value
	HRS-D < 20 (n = 20)	HRS-D ≥ 20 (n = 55)	
Depressive			
Fatigue	1.70 (0.73)	1.65 (0.70)	.81
Agitation*	0.68 (0.67)	1.24 (0.69)	.004
Headache	0.65 (0.75)	0.75 (0.75)	.63
Confusion	0.45 (0.60)	0.80 (0.78)	.07
Hallucinations	0.00 (0.00)	0.06 (0.23)	.29
Total depressive score	3.6 (1.3)	4.5 (1.8)	.07
Physical			
Thirst	0.40 (0.50)	0.63 (0.56)	.11
Palpitations	0.60 (0.82)	0.69 (0.72)	.64
Dry mouth	0.40 (0.50)	0.60 (0.66)	.22
Dizziness†	0.25 (0.55)	0.60 (0.63)	.03
Perspiration	0.40 (0.50)	0.46 (0.57)	.70
Nausea†	0.20 (0.41)	0.58 (0.71)	.03
Tremor	0.25 (0.55)	0.47 (0.60)	.15
Constipation	0.35 (0.59)	0.47 (0.69)	.15
Blurred vision	0.30 (0.57)	0.38 (0.49)	.54
Slurred speech†	0.05 (0.22)	0.27 (0.45)	.04
Urinary difficulty	0.05 (0.22)	0.11 (0.37)	.49
Total physical score†	3.3 (2.4)	5.3 (3.6)	.02
Total symptom score*	6.7 (3.5)	9.8 (4.5)	.007

*Significant at $p < .01$.

†Significant at $p \leq .05$.

Table 2 details the frequency and intensity with which study patients experienced specific depressive and physical symptoms at the time they were prescribed NT. The data indicate that complaints usually considered side effects of this medication were already mildly troublesome to patients. Pharmacotherapists judged approximately half of the cohort as experiencing thirst, palpitations, dry mouth, and dizziness; a minority were already troubled by other physical symptoms resembling NT side effects. As for depressive-like symptoms that also have been construed as possibly resulting from the tricyclic medication, the majority of subjects were judged at baseline as already experiencing them. Indeed, pharmacotherapists rated virtually all of the subjects as displaying fatigue of mild-to-moderate severity before starting treatment with NT.

Next, we analyzed whether the presence of various symptoms resembling tricyclic side effects was related to overall severity of the depressive episode. Depressive severity on the HRS-D was unrelated to four of the five depressive symptoms rated on the Somatic Symptom Checklist after dichotomizing total HRS-D scores according to the previously described convention,³⁰ indicating mild-to-moderate symptomatology (≤ 20) and more severe symptomatology (≥ 20) (Table 3). However, patients with more distressing depressive symptoms at baseline (HRS-D ≥ 20) were significantly more likely to experience physical symptoms than were patients with a milder episode of major depres-

sion (HRS-D ≤ 19). These physical symptoms were particularly marked among patients with a previous history of panic disorder. They experienced significantly more agitation, nausea, tremor, and slurred speech than did patients lacking this pattern of comorbid Axis I disorder.

The unpleasant side effects of a tricyclic antidepressant medication are thought to promote premature termination of pharmacotherapy. Therefore, we considered whether the dropout subgroup ($n = 25$) differed from the treatment completers with regard to baseline symptom patterns. We found no differences between the subgroups in their scores on the five-item depressive symptom cluster or in their total scores on the Somatic Symptom Checklist (Table 4). However, scores on the 11-item physical symptom cluster of the Somatic System Checklist were significantly higher for the dropouts than for treatment completers. Thus, before starting on NT, the patients who later terminated pharmacotherapy prematurely were already experiencing mild nausea, tremor, and slurred speech, whereas these symptoms were relatively absent among treatment completers.

The final analysis pertains to the clinical course of symptoms assessed at baseline, the point of stability, and at the last continuation-phase session in which the patient participated. We found that all symptoms in the depressive cluster, with the exception of hallucinations (experienced by only 4% of patients at baseline) diminished

Table 4. Relation of the Baseline Somatic Symptom Checklist Score to Adherence with Acute-Phase Pharmacotherapy for Major Depression

Symptom	Mean Symptom Score (SD)		p Value
	Dropout (n = 25)	Completer (n = 50)	
Depressive			
Fatigue	1.48 (0.77)	1.76 (0.66)	.10
Agitation	1.16 (0.75)	1.06 (0.72)	.58
Headache	0.76 (0.78)	0.70 (0.74)	.75
Confusion	0.72 (0.68)	0.70 (0.79)	.91
Hallucinations	0.08 (0.28)	0.02 (0.14)	.20
Total depressive score	4.1 (2.1)	4.3 (1.5)	.67
Physical			
Thirst	0.58 (0.50)	0.56 (0.58)	.87
Palpitations	0.64 (0.70)	0.68 (0.77)	.83
Dry mouth	0.52 (0.65)	0.56 (0.61)	.79
Dizziness	0.56 (0.71)	0.48 (0.58)	.60
Perspiration	0.52 (0.51)	0.40 (0.57)	.38
Nausea*	0.80 (0.76)	0.32 (0.55)	.003
Tremor†	0.64 (0.64)	0.30 (0.54)	.02
Constipation	0.64 (0.81)	0.34 (0.56)	.06
Blurred vision	0.44 (0.51)	0.32 (0.51)	.34
Slurred speech†	0.36 (0.49)	0.14 (0.35)	.03
Urinary difficulty	0.08 (0.45)	0.13 (0.27)	.60
Total physical score†	5.8 (4.0)	4.2 (2.9)	.04
Total symptom score	10.1 (5.5)	8.4 (3.7)	.12

*Significant at $p < .01$.

†Significant at $p \leq .05$.

significantly in intensity from baseline to the point of stability (Table 5). This pattern was also evident for several physical cluster symptoms. Furthermore, these clinical improvements extended beyond the point of stability to the last session attended by the patient. As a result, scores for both depressive and physical symptom clusters, as well as total score on the Somatic Symptom Checklist, were reduced significantly with the passage of time. Only symptoms of dry mouth increased from baseline levels to the point of stability. However, this symptom declined during the continuation phase of pharmacotherapy to a level approaching baseline.

DISCUSSION

As in earlier reports about primary care patients,¹⁷⁻¹⁹ our analyses support the observation that somatic symptoms resembling side effects of tricyclic antidepressants are often present among depressed primary care patients before the initiation of pharmacotherapy. In addition, we found patients with more severe depressive symptoms and those with a comorbid panic disorder to experience higher levels of somatic symptoms resembling tricyclic side effects before initiating pharmacotherapy than other depressed individuals. Furthermore, those who experienced higher levels of physical symptoms at baseline were less likely to adhere to the prescribed antidepressant regimen and

more likely to drop out of the acute phase of pharmacotherapy. Still, those depressed patients who reached a point of stability experienced significant reductions among a variety of depressive and physical symptoms, which continued to decline in severity through the continuation phase of tricyclic antidepressant pharmacotherapy.

This report is the first to describe changes in somatic symptoms resembling tricyclic side effects among depressed primary care patients completing the acute phase of antidepressant therapy. It extends our understanding of the course of these somatic symptoms beyond the time frame previously reported for depressed psychiatric,^{13,15} geriatric,¹⁶ or primary care patients.¹⁸ Our findings clearly support the concept that treatment of the underlying depressive episode can reduce the number and severity of depression-associated somatic symptoms experienced by primary care patients.

It is not surprising that patients with more severe depressive symptoms and those with a comorbid panic disorder experienced more distressing subjective symptoms before the initiation of antidepressant therapy. This is consistent with previous reports describing a relation between depression and somatization disorder.³⁸⁻⁴⁰ It also highlights the need for clinicians to consider comorbid psychiatric diagnoses when evaluating patients with multiple physical ailments that seemingly lack an obvious underlying physical cause.³⁸

Table 5. Changes in Mean Somatic Symptom Checklist Score Over Time for Patients Completing Acute Phase Pharmacotherapy (n = 43)*

Symptom	Mean Symptom Score (SD)			Significance Testing Paired Comparisons			
	Time 1 Baseline	Time 2 Point of Stability	Time 3 Last Session	Overall p	1 vs 2 p	2 vs 3 p	1 vs 3 p
Depressive							
Fatigue [†]	1.77 (0.68)	0.58 (0.79)	0.44 (0.67)	<.001	<.001	.37	<.001
Agitation [†]	1.07 (0.68)	0.29 (0.55)	0.38 (0.66)	<.001	<.001	.46	<.001
Headache [†]	0.74 (0.73)	0.21 (0.51)	0.40 (0.66)	.001	<.001	.16	.03
Confusion [†]	0.71 (0.80)	0.21 (0.47)	0.12 (0.40)	<.001	.001	.29	<.001
Hallucinations	0.02 (0.15)	0.24 (0.15)	0.00 (0.00)	.61	—	—	—
Total depressive score [†]	4.4 (1.5)	1.4 (1.5)	1.3 (1.3)	<.001		.94	<.001
Physical							
Thirst	0.47 (0.55)	0.67 (0.57)	0.51 (0.59)	.15	—	—	—
Palpitations [†]	0.72 (0.80)	0.09 (0.37)	0.19 (0.39)	<.001	<.001	.21	<.001
Dry mouth [†]	0.56 (0.63)	0.98 (0.46)	0.58 (0.66)	<.001	.001	<.001	.88
Dizziness [‡]	0.47 (0.59)	0.30 (0.60)	0.19 (0.50)	.03	.13	.30	.006
Perspiration	0.37 (0.54)	0.44 (0.59)	0.30 (0.56)	.48	—	—	—
Nausea [†]	0.30 (0.51)	0.09 (0.37)	0.07 (0.26)	.004	.02	.66	.006
Tremor	0.26 (0.49)	0.16 (0.37)	0.07 (0.26)	.07	—	—	—
Constipation	0.30 (0.51)	0.35 (0.61)	0.16 (0.43)	.18	—	—	—
Blurred vision [‡]	0.30 (0.51)	0.12 (0.39)	0.07 (0.26)	.02	.07	.53	.006
Slurred speech	0.09 (0.29)	0.02 (0.15)	0.00 (0.00)	.07	—	—	—
Urinary difficulty	0.07 (0.26)	0.05 (0.21)	0.00 (0.00)	.25	—	—	—
Total physical score [†]	3.9 (2.7)	3.3 (2.0)	2.1 (2.5)	.001	.14	.01	.001
Total symptom score [†]	8.2 (3.6)	4.6 (2.7)	3.5 (3.3)	<.001	<.001	.04	<.001

*Mean number of weeks from baseline to point of stability is 8.0 (SD 3.5) from baseline to last session is 28.0 (SD 10.9).

[†]Overall score significant at $p < .01$.

[‡]Overall score significant at $p \leq .05$.

Tricyclic pharmacotherapy is often used by clinicians when initiating depression specific treatment³⁹⁻⁴¹ because of its well-established efficacy and low direct cost to patients.⁶ Yet, somatic complaints following the initiation of tricyclic pharmacotherapy remain a significant management problem. Although generally better tolerated by patients than tricyclic medications, pharmacotherapy with a serotonin reuptake inhibitor, bupropion, venlafaxine, or nefazodone nevertheless poses a similar management challenge.⁴² As a result, physicians must frequently decide whether a patient's continued symptoms are related to the medication or the underlying depression. Although primary care physicians presumably altered their antidepressant prescribing practices as a result of patients' depressive symptoms, we did not assess whether this in fact occurred. Therefore, we suggest that future studies investigate the relation between patients' depressive symptoms and clinicians' choice and management of antidepressant drugs.

Symptoms that are true medication side effects would be expected to either appear or increase in severity from the start of drug treatment. Yet, of all the "typical" side effect symptoms we investigated that have been associated with tricyclic medications, only symptoms of dry mouth increased significantly from the start of treatment to the end of the acute phase of depression therapy. This finding

resembles other reports of patients recovering from depression using tricyclic antidepressants.^{13,16,18} Furthermore, we found that the severity of these dry mouth symptoms declined during continuation therapy to approach that found before commencing pharmacotherapy.

Given the typical delay before tricyclic medications exert an antidepressant impact and reduce the severity of depressive symptoms, physicians may inadvertently underdose, discontinue, or change the class of antidepressant pharmacotherapy before allowing completion of an adequate therapeutic trial. In addition, individuals who are not strongly motivated to continue with therapy may become discouraged and discontinue treatment prematurely.⁴² Better awareness of the somatic effects of major depression, consequences of therapy, and course of symptoms may result in better management of both physicians' and patients' expectations regarding antidepressant pharmacotherapy. Such knowledge may also significantly improve medication adherence and subsequent treatment outcomes.²¹⁻²⁴

The generalizability of our findings to patients typically encountered in primary care settings is limited by features of the randomized control trial such as the several assessment phases used to establish subjects' protocol eligibility. Although our study subjects had a higher

level of depressive severity and lifetime prevalence of panic disorder than do depressed patients typically encountered in primary care settings, their lifetime prevalence of anxiety disorders was similar to those uncovered by other investigators.⁴³⁻⁴⁵ Furthermore, information on subjective symptoms resembling tricyclic side effects was collected only on study subjects randomized to NT and not among the "usual care" control subjects. Our attrition rate could have been influenced by patients who were randomized to receive NT but did not wish to receive pharmacotherapy, and by the use of trained pharmacotherapists who were not the patients' usual primary care physicians. Still, the percentage of treatment dropouts in our study resembles that in other large prospective trials of treatment interventions for major depression in primary care settings.^{9,10} Although our study monitored NT serum levels to individualize medication doses and assess medication adherence, we lacked objective physical data, such as pulse and weight changes, to correlate with our study patients' subjective symptoms. Also, information regarding subjects' previous experience with tricyclic antidepressants was not collected. Nevertheless, our findings resemble those in previous studies of somatic symptoms among depressed patients.^{13-15,36,46}

The presence of symptoms resembling tricyclic side effects in depressed primary care patients does not appear to contraindicate the initiation of tricyclic pharmacotherapy. Clinicians should consider their patients' somatic complaints within the clinical context in which they occur before attributing them to their medications. Persistent somatic symptoms or side effects such as dry mouth should be minimized using a variety of accepted strategies,⁴⁷ before attempting to change therapy. As with other medical conditions, the ideal strategy for reducing patients' distress remains the proper treatment of the underlying illness. Our findings, which characterize the symptoms of major depression and their course under treatment, may promote the use of adequate dosages and durations of pharmacotherapy and, as a result, facilitate primary care patients' recovery.

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