Efficacy of Sertraline in Prevention of Depression Recurrence in Older Versus Younger Adults With Diabetes

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OBJECTIVE — Sertraline maintenance therapy effectively delays recurrence of major depressive disorder in adult diabetic patients when data are examined across all age-groups. A secondary analysis was performed to assess this effect in younger and older subsets of patients.

RESEARCH DESIGN AND METHODS — Younger (aged <55 years, $n = 85$) and older (aged ≥55 years, $n = 67$) subsets were identified from a multicenter, double-blind, placebo-controlled, maintenance treatment trial of sertraline in diabetic participants who achieved depression recovery with open-label sertraline treatment. Cox proportional hazards models were used to determine differences in time to depression recurrence between treatment arms (sertraline or placebo) for each age subset and between age subsets for each treatment.

RESULTS — In younger subjects, sertraline conferred significantly greater prophylaxis against depression recurrence than placebo (hazard ratio 0.37 [95% CI 0.20–0.71]; $P = 0.003$). Benefits of sertraline maintenance therapy were lost in older participants (0.94 [0.39–2.29]; $P = 0.89$). There was no difference in time to recurrence for sertraline-treated subjects between age subsets ($P = 0.65$), but older subjects had a significantly longer time to recurrence on placebo than younger subjects ($P = 0.03$).

CONCLUSIONS — While sertraline significantly increased the time to depression recurrence in the younger diabetic participants, there was no treatment effect in those aged ≥55 years because of a high placebo response rate. Further research is necessary to determine the mechanisms responsible for this effect and whether depression maintenance strategies specific for older patients with diabetes should be developed.

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The prevalence of diabetes increases with age. Rates are double those found in the general adult population, with 10.3 million (20.9%) older adults carrying the diagnosis (1). Depression affects one in four patients with diabetes (2) and causes diminished quality of life (3), increased health care utilization and expenditures (4,5), and disability (6). There are several reasons for high rates of comorbidity. The psychiatric illness not only can result from the hardships of diabetes but also serves as an independent risk factor for the development of type 2 diabetes (possibly through increased insulin resistance) (7) and confers accelerated risk of diabetes complications (8,9), hyperglycemia (10), and mortality (11,12).

Despite the prevalence of comorbid depression and diabetes in older adults, there have been no pharmacologic treatment trials specifically examining the treatment of depression in this group. This is not surprising, as the elderly remain underrepresented in depression treatment trials (13). When adults of all ages with diabetes are studied together, depression responds acutely to pharmacotherapy and psychotherapy (14–17), with depression management resulting in amelioration of both mood and glycemic control (9,15,16). These effects are often transient, as depression in diabetes appears to be highly recurrent (18,19). Only 40% of depressed diabetic patients remain depression free in the year following successful treatment of depression (20).

Maintenance antidepressant trials in general psychiatric populations (without diabetes) demonstrate the efficacy of antidepressants in prolonging the depression-free interval, decreasing depression recurrence rates by ~30% over 3 years (16,21–26). Similar data in older subjects are limited, and results are inconclusive (27–29). We recently conducted a double-blind, placebo-controlled, multicenter, two-phase clinical trial of sertraline for treatment of depression in patients aged 18–76 years with comorbid diabetes and depression (16). In the induction phase, patients with major depressive disorder (MDD) received 16 weeks of open-label treatment with sertraline. In the subsequent maintenance phase, participants who achieved depression recovery on sertraline were randomized to sertraline or placebo for 52 weeks or until depression recurred. Patients receiving sertraline experienced a statistically significant increase in the duration of the depression-free interval. Younger age was an independent predictor of de-

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Abbreviations: BDI, Beck Depression Inventory; MDD, major depressive disorder.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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pression recurrence in the initial report, but the finding was not explored beyond the simple reporting of this effect.

The purpose of the current study was to examine the effect of sertraline on the prevention of MDD recurrence in subsets of younger (aged <55 years) and older (aged ≥55 years) patients with diabetes who initially had responded to open-label sertraline for induction of depression recovery, utilizing a secondary analysis of our previously published data. We hypothesized that sertraline would be equally effective in each age-group, providing the first evidence for the use of pharmacotherapy for maintenance of the depression-free interval in older patients with diabetes.

RESEARCH DESIGN AND METHODS

— This report presents a secondary analysis of younger (aged <55 years) and older (aged ≥55 years) subjects completing maintenance treatment with sertraline or placebo in a previously reported clinical trial (20). This age cut point was selected because it represented an approximate mean split, was the 5-year increment closest to the mean age of the sample (52.8 ± 12.3 years), and provided a balanced number of subjects in each treatment arm within age-groups. Although a cut point of 65 years of age may have better partitioned a geriatric population, the resultant distribution and numbers of participants would have prohibited full statistical analysis. Nevertheless, the pattern of principal findings also was examined at older age cut points.

The parent study was a multicenter, two-phase depression treatment trial involving the collaboration of Washington University, St. Louis; the University of Arizona, Tucson; and the University of Washington, Seattle. Inclusion criteria were age 18–80 years, diagnosis of type 1 or type 2 diabetes (per patient self-report with diagnosis confirmation by primary physician), diagnosis of MDD as defined in the DSM-IV (1), and a total score of ≥14 on the Beck Depression Inventory (BDI) (12) or ≥15 on the Hamilton Depression Rating Scale (30). The Depression Interview and Structured Hamilton was used to extract symptoms required for the diagnosis of MDD (31). Patients with active suicidal or homicidal ideation, prior suicide attempt, active alcohol or other substance abuse, history of psychotic disorder, history of bipolar disorder, or contraindication to use of sertraline were excluded. Informed consent to participate was obtained from all subjects before evaluation. The institutional review board at each study site reviewed and approved the trial. The methods for the study have been previously described (16).

In the parent study, 389 patients were evaluated for study inclusion, and 351 (90.2%) met all eligibility requirements, enrolled in the trial, and initiated open-label treatment with 50 mg sertraline every morning. The dose of sertraline was adjusted based on clinical response and tolerability to a maximum dose of 200 mg daily. The current report focuses on the 152 subjects who achieved depression recovery during the induction phase and who randomly were assigned to sertraline at the dosage required to achieve recovery or to placebo. Each subject was followed for 52 weeks or until depression recurred. Recovery from depression was defined according to DSM-IV criteria (1) as a period of at least 2 months, during which there were no significant symptoms of depression, and was operationally defined as four consecutive twice-monthly BDI scores of nine or less within 4 months of beginning sertraline and subsequent confirmation of the absence of major depression by diagnostic reevaluation.

Monitoring during maintenance treatment

Subjects were evaluated at the office each month and via telephone interview at the midpoint between each office visit. The BDI was repeated at office visits, and a brief depression severity assessment was performed during telephone interviews (20). Two consecutive BDI scores of ≥10, a single score ≥16 (32), or detection of recurrent, sustained depression symptoms by telephone assessment prompted a psychiatric interview with the Depression Interview and Structured Hamilton (31). DSM-IV criteria were used to define recurrence of MDD. Subjects with depression recurrence were referred out of the study for depression treatment. Study personnel conducting the depression assessments were blinded to treatment assignment.

As a means to assess glycemic control, A1C levels were measured every 2 months until the time of study completion or depression recurrence. Because of the time period incorporated in a single A1C measurement and the brief interval between depression assessments, all values obtained following randomization were considered reflective of the depression-free interval following depression recovery (2).

Statistical methods

Differences in demographic and clinical characteristics of subjects stratified by age <55 or ≥55 years and randomized to sertraline or placebo were analyzed with intention-to-treat methods utilizing the Fisher's exact test for categorical data and the Student's *t* test for continuous data. Comparison of the time to recurrence of MDD between treatment arms for each age-group was the primary analysis using the log-rank statistics from Kaplan-Meier curves. Subjects who failed to complete the protocol were censored at their time of discontinuation. Similar analyses were used to compare the time to recurrence within each treatment arm when subgroups were stratified by age. Cox proportional hazards models were used in the primary analyses to calculate hazards ratios (HRs) for the treatment effects when controlling for intergroup differences in baseline variables. Cox models also were used in secondary analyses to determine independent predictors of depression recurrence within each age-group. Two sets of variables were included in each of these secondary analyses: the first comprised predictors of depression recurrence in psychiatric samples (age, sex, marital status, and total BDI score at baseline), and the second consisted of aspects of diabetes that may predispose patients to recurrent depression episodes (type of diabetes, duration of diabetes, and baseline A1C level). All predictor variables were included without stepwise elimination, and a $P < 0.05$ was required for a significant independent contribution.

An average of A1C levels beyond the randomization value was computed for each subject over the depression-free interval during maintenance therapy (20). To examine the effect of maintenance treatment on glycemic control, A1C levels at baseline (immediately before the start of open treatment) were compared with the average derived from the depression-free interval using a paired *t* test. BDI values were computed and compared in the same fashion, with the exception that the recurrence value was not used in calculating mean BDI over depression-free interval.

RESULTS

— Of 351 patients with diabetes who entered the induction phase of the parent study, 156 (44%) achieved depression recovery (20). Four withdrew,

Table 1—*Demographics of the sample in relation to age subset and maintenance treatment arm*

	Younger subjects (aged <55 years)			Older subjects (aged ≥55 years)		
	All	Sertraline	Placebo	All	Sertraline	Placebo
n	85	47	38	67	32	35
Age (years)	44.0 ± 7.7	43.0 ± 8.1	45.3 ± 7.1	64.0 ± 6.6	61.5 ± 6.2*	66.3 ± 6.2
Female sex	50 (58.8)	27 (57.4)	23 (60.5)	41 (61.2)	19 (59.4)	22 (62.9)
White race	69 (81.2)	36 (76.6)	33 (86.8)	54 (80.6)	26 (81.3)	28 (80.0)
Married	55 (64.7)	31 (66.0)	24 (63.2)	36 (53.7)	13 (40.6)	23 (65.7)
Education (years)	14.3 ± 2.4	14.2 ± 2.6	14.5 ± 2.1	13.9 ± 2.9	14.2 ± 2.8	13.5 ± 2.9
Type 2 diabetes	60 (70.6)	32 (68.1)	28 (73.7)	66 (98.5)	32 (100)	34 (97.1)

Data are means ± SD or *n* (%). *$P = 0.003$ compared with placebo-treated subjects.

leaving 152 subjects for study in this secondary analysis. Demographics and disease characteristics of the younger and older subsets stratified by treatment arm are presented in Tables 1 and 2. Of 85 younger subjects (aged <55 years), 47 were assigned to sertraline and 38 to placebo. There were no significant differences between treatment arms for any of the variables shown in the tables for this age-group. Of 67 participants aged ≥55 years, 32 received sertraline and 35 received placebo. Those receiving sertraline were slightly younger and had greater likelihood of prior depression treatment. The average sertraline dose was comparable for the two age-groups: 116 mg daily for older and 118 mg daily for younger subjects. Twenty-two of 152 subjects (14.5%) did not complete the maintenance protocol. Noncompleters were younger than completers (47.9 ± 13.1 vs. 53.6 ± 12.0 years; $P = 0.045$), and the proportion of African Americans was greater in the noncompleter group (36.4 vs. 16.2%; $P = 0.038$).

Kaplan-Meier plots for time to depression recurrence are shown for each treatment arm in younger and older age-groups in Fig. 1. In younger subjects, there was a significant treatment effect of sertraline in prolonging the depression-free interval ($\chi^2 = 9.67$, df = 1, $P = 0.002$). HRs were calculated from the Cox models with no covariates required for this age-group (HR 0.37 [95% CI 0.20–0.71]; $P = 0.003$). The time elapsed before one-third of the younger subjects recurred increased from 53 days for placebo-treated to 284 days for sertraline-treated subjects (a 231-day difference). At 1 year, rates of sustained depression re-

Table 2—*Depression and diabetes characteristics of the sample in relation to age subset and maintenance treatment arm*

	Younger subjects (aged <55 years)			Older subjects (aged ≥55 years)		
	All	Sertraline	Placebo	All	Sertraline	Placebo
n	85	47	38	67	32	35
Age of depression onset (years)	28.5 ± 12.3	26.9 ± 12.4	30.4 ± 12.0	37.4 ± 19.0	34.6 ± 15.6	39.9 ± 21.6
Number of prior episodes of depression	5.0 ± 7.7	5.7 ± 9.7	4.3 ± 5.1	4.2 ± 3.8	5.2 ± 4.6	3.5 ± 2.9
Family history of depression*	39 (54.2)	21 (50.0)	18 (60.0)	26 (44.1)	12 (41.4)	14 (46.7)
Prior depression treatment*	41 (51.9)	21 (48.8)	20 (55.6)	38 (61.3)	22 (75.9)†	16 (48.5)
BDI at baseline	21.2 ± 6.9	21.0 ± 6.9	21.5 ± 6.9	22.1 ± 6.5	22.7 ± 6.7	21.6 ± 6.3
BDI at randomization	4.0 ± 2.6	4.4 ± 2.9	3.4 ± 2.1	4.0 ± 3.2	4.4 ± 3.3	3.5 ± 3.1
HDRS at baseline	16.2 ± 4.5	16.3 ± 4.9	16.0 ± 4.1	15.3 ± 4.2	14.8 ± 3.3	15.8 ± 3.5
HDRS at randomization	3.7 ± 3.3	3.3 ± 2.8	4.1 ± 3.9	3.5 ± 2.8	3.2 ± 2.4	3.8 ± 3.1
Sertraline dose at recovery (mg/day)	118 ± 52	120 ± 55	116 ± 50	116 ± 53	116 ± 56	117 ± 51
Age of diabetes onset (years)	33.7 ± 12.1	32.8 ± 11.5	35.0 ± 12.8	55.1 ± 11.2	52.7 ± 10.7	57.3 ± 11.3
Duration of diabetes (years)	10.8 ± 9.9	10.5 ± 9.7	11.2 ± 10.2	8.2 ± 8.3	7.8 ± 8.7	8.6 ± 8.0
Diabetes complications						
Neuropathy	37 (43.5)	25 (53.2)	12 (31.6)	31 (46.3)	11 (34.4)	20 (57.1)
Nephropathy	10 (11.8)	6 (12.8)	4 (10.5)	6 (9.0)	3 (9.4)	3 (8.6)
Retinopathy	15 (17.6)	9 (19.1)	6 (15.8)	18 (26.9)	10 (31.3)	8 (22.9)
Atherosclerotic	8 (9.4)	4 (8.5)	4 (10.5)	14 (20.9)	7 (21.9)	7 (20.0)
Diabetes management						
Diet only	6 (7.1)	3 (6.4)	3 (7.9)	10 (14.9)	7 (21.9)	3 (8.6)
Insulin	38 (44.7)	20 (42.6)	18 (47.4)	16 (23.9)	8 (25.0)	8 (22.9)
Oral agent	29 (34.1)	18 (38.3)	11 (28.9)	34 (50.7)	14 (43.8)	20 (57.1)
Insulin and oral agent	12 (14.1)	6 (12.8)	6 (15.8)	7 (10.4)	3 (9.4)	4 (11.4)
A1C at baseline (%)	8.6 ± 1.8	8.5 ± 1.8	8.7 ± 1.7	7.7 ± 1.5	7.7 ± 1.5	7.7 ± 1.6
A1C at randomization (%)	8.0 ± 1.7	8.2 ± 1.8	7.9 ± 1.6	7.6 ± 1.4	7.4 ± 1.1	7.7 ± 1.7

Data are means ± SD or *n* (%). *Provided for those subjects with available data. †$P = 0.04$ compared with placebo-treated subjects. HDRS, Hamilton Depression Rating Scale.

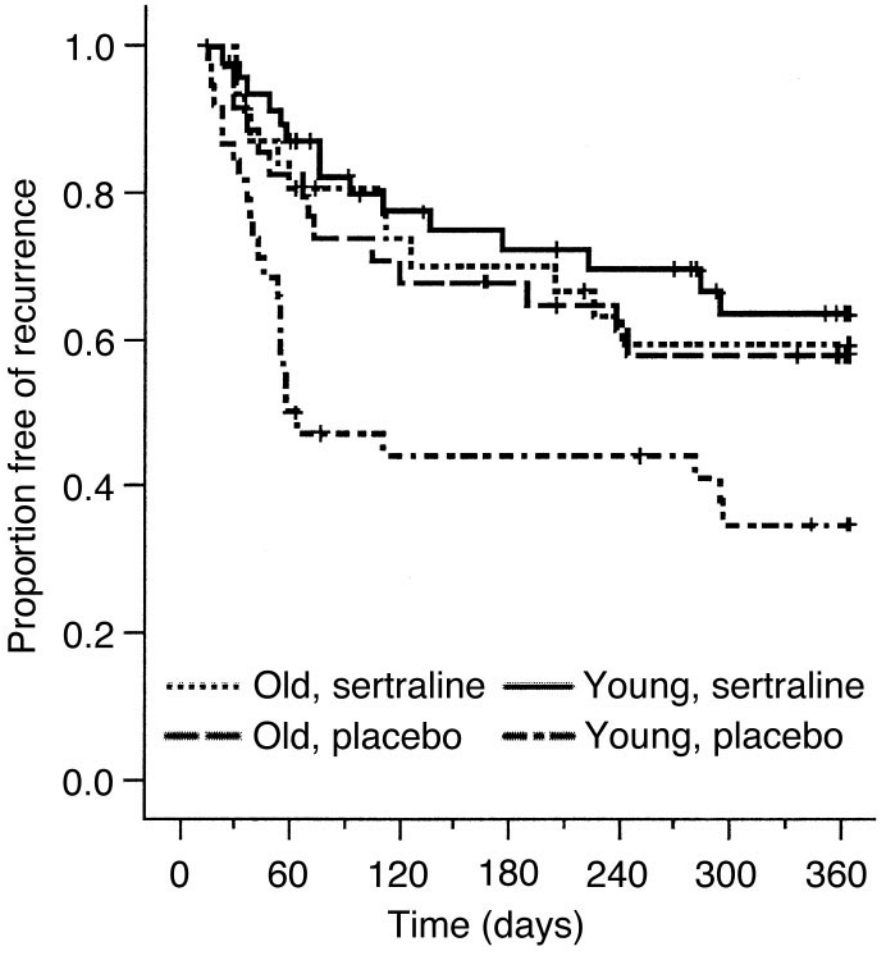

Figure 1—*Kaplan-Meier plots in younger (aged <55 years) and older subjects (aged ≥55 years) showing the proportion remaining free of depression recurrence over time in relation to treatment arm (following initial recovery with open-label sertraline therapy). The time to recurrence was significantly longer with sertraline than placebo in the younger age-group (*P *= 0.002) but was no different in the older subjects (*P *= 0.85).*

mission in the younger subset were 63.4% for subjects on sertraline versus 34.8% for those treated with placebo.

In contrast, there was no significant treatment effect of sertraline in the older subjects ($\chi^2 = 0.035$, df = 1, $P = 0.85$), a finding that was unchanged when the analysis was controlled for intergroup differences in age and rate of prior depression treatment (HR 0.94 [95% CI 0.39–2.29]; $P = 0.89$) (Fig. 1). Elapsed time before one-third of subjects recurred only increased from 168 days for older subjects on placebo to 205 days for the subset on sertraline (37-day difference). At 1 year, rates of sustained depression remission in the older subset were 59.2% for subjects on sertraline versus 57.8% for those treated with placebo. The pattern of findings was statistically similar when thresholds of ≥60 years and ≥65 years of age were used to define the older subset, with neither analysis showing a significant beneficial effect of treatment ($P > 0.70$ for each log-rank comparison).

Comparison of treatment arms across age-groups revealed that the impact of sertraline on the time to recurrence was no different in younger versus older subjects ($\chi^2 = 0.21$, df = 1, $P = 0.65$). However, the placebo effect was more pronounced in the older group ($\chi^2 = 4.63$, df = 1, $P = 0.03$) (Fig. 1). The differential response to placebo for younger and older groups was not due to a variation in the intensity of placebo interventions for the two cohorts. There was no significant difference in the number of visits attended per month by younger and older subjects. In younger subjects, female sex ($P = 0.03$) predicted shorter time to recurrence independently of treatment, whereas higher baseline BDI ($P < 0.001$) was an independent predictor in older subjects.

Pretreatment A1C levels were lower in older compared with younger subjects (7.7 ± 1.5% vs. 8.6 ± 1.8%, $P = 0.001$). During the depression-free interval of maintenance treatment, A1C levels improved relative to baseline in younger subjects (−0.5 ± 1.4%, $P = 0.001$ compared with baseline) yet did not significantly change in older subjects (−0.2 ± 1.3%, $P = 0.27$).

CONCLUSIONS— This secondary analysis demonstrates a robust advantage of sertraline over placebo in the prevention of depression recurrence for younger participants with diabetes. The time elapsed until depression recurrence for one-third of younger subjects assigned to sertraline maintenance treatment was five times that observed for those randomized to placebo (284 vs. 53 days). In contrast, no difference in time to recurrence for sertraline- versus placebo-treated subjects was found in the older subset. Thus, the treatment response previously observed in the general study population (16) was driven by the younger subset of participants. Time to depression recurrence for older subjects assigned to sertraline was comparable with that observed for younger subjects. However, the older subset demonstrated a significantly better placebo response compared with their younger counterparts, seemingly limiting the value of maintenance pharmacotherapy in the subjects aged ≥55 years.

Subjects in the placebo arm of this study did not experience a therapeutic environment that emulated real-world depression management, a methodological factor that influences the interpretation of the findings. These subjects received telephone and office follow-up visits on a frequent basis. Time constraints imposed on primary care physicians, the health care providers most likely to evaluate and manage older patients with depression symptoms (12), prevent lengthy interactions with patients or the meticulous, frequent follow-up visits permitted in depression treatment trials like the present one. It is possible that the elevated placebo response in the older subset reflects the therapeutic benefit of these interactions, a benefit to which older adults may be more inclined. Nonpharmacological interventions, specifically intensive supportive measures, may be as effective as pharmacotherapy for prevention of depression recurrence in this age-

group after depression recovery initially is accomplished. As older adults experience a higher rate of adverse drug effects and have higher rates of polypharmacy (24), the potential to maintain lasting depression remission via nonpharmacological means would be appealing.

Once the treatment effect of sertraline was taken into consideration, the Cox proportional hazard models found that female sex was a predictor of recurrence in the younger subjects. In two naturalistic studies (19,20) of depression in diabetic patients, we did not find that women conspicuously were more predisposed to recurrent depression episodes than men, but few men were in the study and age-groups were not examined separately. In studies of patients without diabetes, sex typically is not an independent predictor of depression course, even in early-onset disease (33,34). Thus, this finding requires replication in other studies. Higher baseline BDI was an identified predictor of recurrence in our older subjects in whom there was no significant treatment effect of the medication tested. Having a higher degree of baseline depression symptoms is an acknowledged risk factor for recurrence. Its ability to do so was uncovered in this age subgroup that lacked a treatment effect overpowering conventional risks.

Younger diabetic patients had higher pretreatment A1C levels than their older counterparts and demonstrated improved glycemic control during the depression-free interval. The latter observation parallels some (14,35,36), albeit not all (37,38), prior reports that amelioration of depression symptoms can result in early and sustained improvement in A1C levels. Curiously, the older participants in our study were in better glycemic control than subjects in most prior studies of comorbid diabetes and MDD, and depression recovery did not impact these values significantly (20,36). Possible explanations include that the lower baseline levels blunted the ability to detect significant change, as there was a trend toward reduction in this group. It also is possible that the biological aspects of depression in this age-group differ from those in younger patients (e.g., with less activation of the hypothalamopituitary adrenal axis and alteration in cortisol homeostasis, which would have less effects on glycemic control and potentially explain differential responsiveness to treatments). Of note, sertraline was not found to have an overt detrimental effect on glycemic control in either age-group, in contrast to the significant hyperglycemic effect of nortriptyline observed in a previous 8-week, acute-phase depression treatment trial of diabetic patients (14). Less endogenous insulin availability (viz., more type 1 diabetic patients) in conjunction with insulin injection and greater glycemic variability (viz., higher A1C) in the younger subset may predispose to recurrence through their proinflammatory associations (39–41). This speculation for the poorer placebo effect in younger subjects is not well supported by the fact that we did not find an effect of diabetes type on the likelihood of recurrence in the parent study (16).

Our study has several strengths and some relevant limitations. Depression management consensus statements indicate that selective serotontin reuptake inhibitors are the recommended drug class for depression treatment in older adults (28), making our observations in the older subset germane to current practice. Sertraline had been selected for the parent study because it is a commonly prescribed antidepressant in primary care settings, but our findings may not be generalizable to other selective serotontin reuptake inhibitors or antidepressant classes. Similarly, the findings from this clinical research study may not be directly comparable with outcomes achieved in primary care. The sample size for the maintenance phase was large enough to provide reasonable numbers in each age-group. However, the study does represent a post hoc secondary analysis and, as such, requires replication in prospective fashion. The mean age of older participants was 64 years, ranging from 55 to 76 years. The applicability of the results to patients only on the more advanced side of this range is unclear (24,27,29), although the analyses of subjects aged ≥60 or ≥65 years did not affect our conclusions. Several other potential limitations of the parent study design have been discussed in the previous report (20).

This study provides the first analysis of maintenance depression therapy in older adults with comorbid diabetes and depression. Results from the present study reveal differences in treatment outcomes in younger and older diabetic subjects managed with sertraline for depression maintenance, the outcomes being influenced by an enhanced response to placebo and the supportive study environment in the older subset. Characteristics other than age (e.g., type of diabetes) separate the two subject groups and may be responsible for the variations in treatment response. Further research is needed to prospectively confirm these findings and to determine whether depression treatment algorithms that are specific for younger and older populations should be developed, especially in patients with comorbid medical illnesses such as diabetes.

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