Discontinuation of Maintenance Selective Serotonin Reuptake Inhibitor Monotherapy After 5 Years of Stable Response: A Naturalistic Study

Tara M. Pundiak, M.D.; Brady G. Case, M.D.;
Eric D. Peselow, M.D.; and Loretta Mulcare, B.S.E.

Objective: Selective serotonin reuptake inhibitors (SSRIs) are effective treatments of major depressive disorder (MDD), but data to guide the duration of maintenance therapy in community settings are limited. We assessed whether extending maintenance beyond 5 years provided additional benefit and identified other predictors of outcome.

Method: All patients treated at an urban community outpatient clinic between June 1993 and September 2005 were considered for inclusion in this study. Based upon patient preference and clinician judgment, 60 patients with DSM-IV MDD elected to continue, and 27 patients to discontinue, SSRI treatment after 5 years of clinical stability on maintenance monotherapy in a community clinic. Differences in relapse risk were assessed using the Kaplan-Meier product limit method, and risk factors were evaluated in Cox proportional hazards regression, based on up to 8 years of illness course.

Results: Subjects who continued on SSRI treatment experienced a survival probability of maintaining remission during the first year, which was twice that of discontinued subjects (0.79 vs. 0.40), and survival differences persisted for over 30 months. Median survival time until relapse for patients who continued SSRIs was 38 months, exceeding the 10-month survival time of patients who discontinued. After controlling for significant covariates, the hazard ratio for SSRI discontinuation was 4.9. Residual depressive symptoms conferred increased relapse risk, while age, gender, SSRI type and dose, and prior depressive episodes did not predict relapse.

Conclusion: After 5 years of maintenance monotherapy for MDD, SSRI discontinuation in a community setting is associated with a far poorer illness course than continued maintenance. Discontinuation of long-term maintenance is most likely to be successful in patients with minimal residual symptoms, and discontinued patients should be carefully monitored.

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Dr. Case is currently with the Department of Adolescent Psychiatry, New York University School of Medicine, New York; and the Statistics and Services Research Division, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, N.Y.

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Corresponding author and reprints: Tara M. Pundiak, M.D., PSC 476 Box 76, FPO, AP 96322 (e-mail: pundit01@med.nyu.edu).

Major depressive disorder (MDD) is common[1,2] and is associated with significant morbidity, mortality, and economic cost.[3–8] The course of MDD is chronic, with up to 85% of patients with 1 major depressive episode suffering from a recurrence in their lifetime.[9]

Selective serotonin reuptake inhibitors (SSRIs) are effective for the treatment of MDD[10] and are currently the most commonly prescribed medications for MDD.[11,12] The American Psychiatric Association's practice guideline[13] indicates SSRIs as first line pharmacotherapy for MDD due to their efficacy, safety, and tolerability. The guideline recommends that following remission of depressive symptoms, antidepressant medication should be continued for 16 to 20 weeks and subsequently maintained for an unspecified duration.

Despite the use of SSRIs for 2 decades,[10] limited data are available to inform selecting the duration of maintenance treatment for MDD in community settings. Randomized clinical trials data[14–28] may not be generalizable to patients encountered in the community, who suffer from comorbid Axis I,[29] personality,[30] and medical disorders[31] excluded from most clinical trials.

Further, existing trial data examine maintenance treatments of no more than 3 years' duration, shorter than may be necessary to treat this chronic illness. The mean number of lifetime depressive episodes in MDD is 5 or 6,[32]

and the time between episodes is variable.[33] Kupfer et al.[34] recommended maintenance treatment of 5 years in recurrent MDD, finding that patients continued on imipramine treatment after 3 years of successful maintenance were markedly less likely to relapse over the subsequent 2 years than those randomly assigned to discontinuation. Outcomes after 5 years of maintenance treatment for MDD, however, have not been available.

We present for the first time naturalistic data on continuation versus discontinuation of maintenance SSRI monotherapy after 5 years of successful treatment for MDD. We sought to address the following questions: (1) does extending maintenance beyond 5 years provide clinical benefit in community settings; and (2) can other risk factors for relapse in long-term maintenance be identified, which may guide clinical decisions about discontinuation?

METHOD

Study Subjects

All patients treated at an urban community outpatient clinic specializing in the treatment of mood and anxiety disorders between June 1993 and September 2005 were considered for inclusion in this study. Subjects provided written informed consent for use of de-identified demographic and clinical data, and the Western Institutional Review Board, Olympia, Wash., approved the use of these data for research purposes. All patients treated in the clinic were diagnosed with DSM-IV[35] MDD upon initial clinic entry by their treating clinician using a modified Structured Clinical Interview for DSM-IV[36] and rated with an initial Montgomery-Asberg Depression Rating Scale (MADRS)[37] score of 18 or greater. Subjects were excluded by current or previous psychotic symptoms in the absence of mood symptoms or bipolar affective disorder, as well as current substance use, pregnancy, or medical illness precluding use of SSRIs. Subjects were of both sexes and ranged in age from 18 to 80.

Selective serotonin reuptake inhibitors included sertraline, paroxetine, and fluoxetine and were chosen on a clinical basis including history of previous response and sensitivity to adverse effects. Other medications used during the study period were benzodiazepines for anxiety < 5 times/mo and trazodone for sleep < 3 times a week.

After 8 to 9 weeks of acute treatment with SSRI monotherapy, subjects met criteria for a response to treatment as measured by a 50% reduction in MADRS score and a final MADRS score of 13 or less. Subjects then entered a 1-month continuation phase followed by a 5-year maintenance phase with SSRI monotherapy. Subjects were subsequently assessed every 3 months for mood symptoms, and clinicians were able to identify any signs or symptoms of recurrence of depression.

After 5 years of clinical stability, SSRI discontinuation was considered for 87 subjects based on patient preference and clinician judgment. After reviewing risks and benefits of SSRI discontinuation with their treating psychiatrist, subjects who elected to continue SSRI maintenance were, for the purpose of this study, considered to have entered the continuation group, while subjects who decided to discontinue were considered to have entered the discontinuation group. Subjects in the discontinuation group underwent SSRI taper over 2 to 5 months and received psychoeducation about signs and symptoms of recurrent mood episodes at taper initiation and sequentially during the taper period.

Table 1. Baseline Characteristics of Patients Continued on or Discontinued From an SSRI After Treatment Response and 5 Years' Maintenance Monotherapy of Major Depressive Disorder[a,b]

Baseline Characteristic	Continued on SSRI Treatment (N = 60)		Discontinued From SSRI (N = 27)		Comparison Analysis		
	Mean	SD	Mean	SD	z	df	p
Age, y	31.7	12.6	34.2	12.8	0.6	1	.56
MADRS score	5.1	4.2	4.3	3.2	–0.5	1	.62
SSRI dose (% of maximum recommended)	79.0	18.9	82.3	20.5	0.5	1	.62
	N	%	N	%	χ^2	df	p
Female	31	51.7	10	37.0	1.6	1	.21
First depressive episode	28	46.7	10	37.0	0.7	1	.40
SSRI medication					0.5	2	.78
Fluoxetine	16	26.7	8	29.6			
Paroxetine	17	28.3	9	33.3			
Sertraline	27	45.0	10	37.0			

[a]MADRS score is the value recorded after 5 years of maintenance treatment.
[b]Groups are compared using the χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.

Clinical Assessments

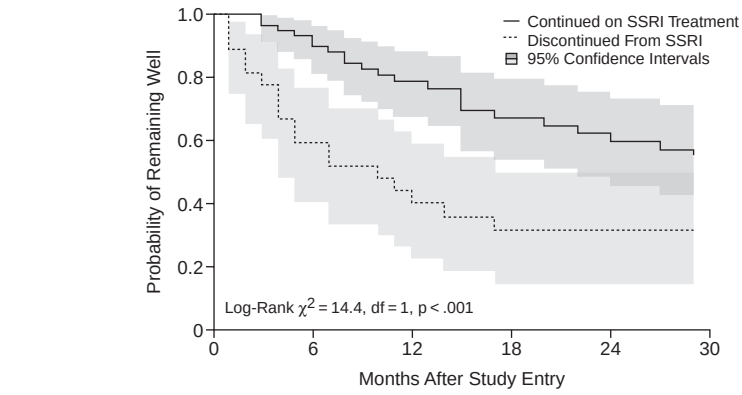
Subjects were assessed every 3 months from study entry for up to 8 subsequent years through 2 possible end points: relapse or a designation of having terminated treatment well. Subjects were considered to have relapsed if they received a MADRS score > 14 rated by the treating psychiatrist and met DSM-IV criteria for a major depressive episode and required either hospitalization or addition or change of medication. Subjects were considered to have terminated well if they did not relapse. Subjects who dropped out and subjects in the medication group who discontinued medication at a later point were considered to have terminated well if they were not relapsed at their final visit.

Data Analysis

Continuation and discontinuation groups were compared for differences in baseline demographic, clinical,

and treatment characteristics using the χ^2 test for categorical variables and Wilcoxon rank sum test—a nonparametric test appropriate where assumptions of large normally distributed samples are not met—for continuous variables. Survival curves with 95% confidence intervals for the 2 groups were generated using the Kaplan-Meier product-limit method and log-log transformation and compared using the log-rank test of homogeneity. Survival probabilities were calculated at 6-month intervals until the number of subjects at risk in either group fell below 5 and were compared during the T test. Differences between these probabilities with 95% confidence intervals were generated using linear survival standard errors. Median survival durations for patient groups were calculated from the Kaplan-Meier survival curves. The 1-year crude relapse rate, a measure less appropriate for survival analysis than Kaplan-Meier failure probability of relapse risk, was calculated for the purpose of comparison to earlier studies.

Figure 1. Kaplan-Meier Estimates of Relapse-Free Survival With 95% Confidence Intervals for Patients Continued on or Discontinued From an SSRI After Treatment Response and 5 Years' Maintenance Monotherapy of Major Depressive Disorder



Number of Patients at Risk						
Continued on SSRI Treatment	60	53	34	28	23	21
Discontinued from SSRI	27	16	10	7	5	5

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

The Cox proportional hazards regression model was used to assess the significance of association between clinical and demographic variables and the hazard function. Included variables are identified in Table 1. Baseline values reflect those on the first visit date after 5 years of maintenance treatment. For the purposes of analysis, baseline MADRS scores were stratified into 3 categories: 0 to 4, 5 to 9, and 10 to 14. Baseline SSRI dose was calculated as a percentage of the maximum manufacturer-recommended SSRI dose. Initial model building included variables significant at the $p < .25$ level in univariate regression, followed by evaluation of interaction effects of relevant variables with medication continuation or discontinuation. All variables were assessed for concordance with the proportional hazards assumption by evaluating interaction of the variables with the log of survival time in the Cox model. Final multivariate Cox regression analysis proceeded in a backwards stepwise fashion with significance set at $p < .05$. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, N.C.).

RESULTS

Baseline Characteristics

Of 87 participants, 60 chose to remain on treatment with an SSRI and entered the continuation group, while 27 chose discontinuation and entered the discontinuation group. There were no significant differences in the demographic or clinical baseline characteristics between the continued versus the discontinued groups at the time of entry (Table 1).

Survival Analysis and Risk Factors

Of 60 patients in the medication continuation group, 27 relapsed, 15 terminated well, and 18 remained well until the end of the study period. Of 27 patients in the discontinuation group, 21 relapsed, none terminated well, and 6 remained well until the end of the study period. Figure 1 shows the 4-year Kaplan-Meier survival curves with 95% confidence intervals for continuation and discontinuation groups, along with the number of patients at risk in each group, over a 30-month period. Patients in the continuation group had a significantly higher chance of remaining well throughout the study ($p < .001$).

The Kaplan-Meier point estimate survival probabilities and unadjusted median survival times are shown in Table 2. Survival probabilities for the continued group exceeded those for the discontinued group through 30 months of follow-up. The median survival time for patients continued on treatment with SSRIs was 38 months, greater than the 10-month median for patients discontinued from SSRIs. Kaplan-Meier failure probability estimates of the relapse risk at each time could be calculated from the survival probabilities (failure probability = 1 – survival probability). The number of patients at risk in the discontinued group fell below 5 before the third year of follow-up. One-year crude relapse rates were 26% (12/46) in the continued and 62% (16/26) in the discontinued groups.

In Cox proportional hazards regression analysis, SSRI discontinuation and higher baseline MADRS scores each contributed significant risk of relapse in the multivariate Cox model (Table 3). The adjusted hazard ratio for SSRI discontinuation was 4.9 ($p < .001$). Compared with baseline point-of entry MADRS scores of 0 to 4, scores of 5 to

Table 2. Survival Probabilities and Median Survival Times With 95% CIs of Patients Continued on or Discontinued From an SSRI After Treatment Response and 5 Years' Maintenance Monotherapy of Major Depressive Disorder[a]

	Continued on SSRI Treatment (N = 60)		Discontinued From SSRI (N = 27)		Comparison Analysis	
Follow-up	Survival Probability	95% CI	Survival Probability	95% CI	Difference	95% CI
6 mo	0.90	0.81 to 0.96	0.59	0.41 to 0.77	0.31	0.11 to 0.51*
12 mo	0.79	0.67 to 0.88	0.40	0.23 to 0.59	0.39	0.17 to 0.60*
18 mo	0.67	0.54 to 0.80	0.31	0.15 to 0.50	0.36	0.14 to 0.58*
24 mo	0.60	0.45 to 0.73	0.31	0.15 to 0.50	0.29	0.06 to 0.52*
30 mo	0.55	0.40 to 0.69	0.31	0.15 to 0.50	0.23	0.00 to 0.47*
	Median	95% CI	Median	95% CI	χ^2	df	p
Survival time, mo	38.0	22.0 to 86.0	10.0	4.0 to 17.0	14.4	1	< .001*

[a]95% CIs for differences between survival probabilities are generated using linear survival standard errors. Median survival times are compared using the log-rank test of homogeneity.
*Statistically significant at $p < .05$.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 3. Hazard Ratios for Characteristics of Patients Continued on or Discontinued From an SSRI After Treatment Response and 5 Years' Maintenance Monotherapy of Major Depressive Disorder[a]

Variable	Hazard Ratio	95% CI	χ^2	df	p
Discontinued from SSRI	4.9	2.5 to 9.7	20.8	1	< .001*
MADRS score at baseline					
0–4[b]	…	…	…	…	…
5–9	4.3	2.1 to 9.1	15.1	1	< .001*
10–14	5.7	2.6 to 12.4	19.0	1	< .001*

[a]Hazard ratios are adjusted for significant risk factors in Cox proportional hazards regression. Significant risk factors are SSRI discontinuation and baseline MADRS score.
[b]Reference group in hazard ratio calculation.
*Hazard ratio significant at $p < .05$.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.

9 were associated with an adjusted hazard ratio of 4.3 ($p < .001$), and scores of 10 to 14 were associated with an adjusted hazard ratio of 5.7 ($p < .001$). Age, gender, SSRI dose and type, and number of prior depressive episodes were not significant predictors of relapse.

DISCUSSION

We found that after 5 years of stability on SSRI monotherapy for MDD, medication discontinuation in a community setting is associated with a far poorer illness course than continued SSRI maintenance. The 27 patients who discontinued medication relapsed, on average, in 10 months, one quarter of the average time to relapse for the 60 patients maintained on SSRI treatment. Probability of remaining free of relapse 1 year after SSRI discontinuation was half that enjoyed by patients maintained on medication, and, controlling for other factors, medication discontinuation was associated with a 5-fold increase in relapse risk over up to 8 years of follow-up.

Our naturalistic findings strengthen placebo-controlled data demonstrating increased relapse risk associated with SSRI discontinuation. Table 4 shows the results of 11 double-blind placebo-controlled studies of SSRI maintenance in MDD.[14–18,20,21,25–28] These studies treated symptomatically depressed patients with SSRI monotherapy in an acute phase; remitters entered a 4 to 8 month continuation phase and were then randomly assigned to placebo or SSRI maintenance for 11 to 28 months. Our hazard ratio of 4.9 for relapse risk after discontinuation is comparable to, although numerically higher than, hazard ratios ranging from 1.21 to 4.07 in these controlled studies. Our high relapse risk may reflect the severity of depressive illness in our naturalistic treatment population, as well as the potential contribution of comorbid anxiety, personality, and medical disorders, which were not excluded from our treatment sample.

Our risk factor analysis suggests that residual depressive pathology, even among patients with long-term response or remission, confers significant risk for relapse. Controlling for medication treatment, patients with baseline MADRS scores of 5 to 9 and 10 to 14 were respectively 4.3 and 5.7 times more likely to relapse than patients with scores of 0 to 4. While Montgomery and Dunbar[22] defined recovery as a score of < 12, others have used different cutoff scores ranging from 13[24,38] to 10.[16,18,27] Our study found increases in risk associated with rising scores within ranges well below conventional recovery cutoffs, suggesting that careful monitoring of even mild residual pathology is crucial in long-term maintenance treatment. Our findings are consistent with correlations between increased risk of recurrence and higher MADRS scores found in some earlier studies.[16,28]

Table 4. Double-Blind, Placebo-Controlled Maintenance Studies of SSRIs in Major Depressive Disorder

Study	Acute Phase			Phase Duration			Maintenance, N		Relapse Rate or Risk		Comparison		
	Medication	Inclusion	Relapse	Acute, wk	Continuation, mo	Maintenance, mo	Medication	Placebo	Medication	Placebo	Log-Rank χ^2	Hazard Ratio	Relative Risk[a]
Doogan and Caillard[14]	Sertraline	HAM-D_{17} > 17	CGI-S > 3	8	0	11	184	105	0.13	0.46	p < .001*	…	(3.54)
Gilaberte et al[15]	Fluoxetine	HAM-D_{17} > 17	HAM-D_{17} > 17	8	6	11	70	70	0.20	0.40	p = .002*	…	(2.00)
Hochstrasser et al[16]	Citalopram	MADRS > 21	MADRS > 21	6–9	4	12–18	132	132	0.18	0.45	p < .001*	3.12*	…
Keller et al[17]	Sertraline	HAM-D_{24} > 17	…	12	4	19	77	84	0.09	0.31	p = .001*	4.07*	…
Klysner et al[18]	Citalopram	MADRS > 21	MADRS > 21	8	16	28	60	61	0.32	0.67	p < .001*	3.13*	…
McGrath et al[20]	Fluoxetine	HAM-D_{17} > 15	HAM-D_{17} > 13	12–14	0	0–12	299	96	…	…	p < .001*	2.22*	…
Montgomery et al[21]	Fluoxetine	HAM-D_{21} > 18	HAM-D_{21} > 18	6	4–5	12	88	94	0.26	0.57	p < .001*	…	(2.19)
Reynolds et al[25]	Paroxetine	HAM-D_{17} > 14	HAM-D_{17} > 14	8	4	~24	35	18	0.34	0.56	p = .02*	…	2.40*
Robert and Montgomery[26]	Citalopram	MADRS > 24	MADRS > 24	8	0	6	152	74	0.14	0.24	p = .04*	…	(1.71)
Terra and Montgomery[27]	Fluvoxamine	MADRS > 25	MADRS > 14	6	4–5	12	110	91	0.13	0.35	p < .001*	2.77*	…
Wilson et al[28]	Sertraline	HAM-D_{17} > 17	HAM-D_{17} > 12	8	4–5	24	56	57	0.45	0.54	p = .21 (NS)	1.21 (NS)	…

[a]Relative risk values in parentheses indicate values calculated for purposes of comparison to other studies by dividing the reported relapse rate or risk for placebo by that for medication. Comparison statistics for these ratios could not be generated.
*Comparison significant at p < .05.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, NS = comparison not significant at p < .05, SSRI = selective serotonin reuptake inhibitor.
Symbol: … = not applicable.

Other clinical characteristics measured in this study were not predictive of course. In particular, our findings strengthen previous data demonstrating that antidepressant dosage is not predictive of relapse in MDD[19,22,26] but do not support work showing that a greater number of depressive episodes predict increased risk of recurrence.[39,40] However, because we characterized episode history categorically as either the absence or presence of prior episodes, our analysis could not detect added risk, which may be associated specifically with highly recurrent illness.

While there are clear benefits to our naturalistic study design, there are also limitations. The patient and clinician decision-making determined SSRI discontinuation, rather than random assignment. While we found no baseline differences between the continued and discontinued groups, unmeasured differences may have confounded the observed association between medication treatment and outcome. Patients who elected to discontinue, and who the treating psychiatrist felt were appropriate for discontinuation, may have been healthier than those in the continued group, erroneously depressing the observed risk of discontinuation. Alternately, patients who elected to discontinue SSRIs may have had less insight into their illness severity, or may have been less committed to treatment, erroneously elevating the observed discontinuation risk. Greater understanding of how patients decide to continue or discontinue successful antidepressant maintenance would enhance our ability to interpret the relative contributions of these potential sources of error and is an important area for future treatment research.

Further, patients in our study were rated by 1 clinician who was not blind to treatment and had a clinical relationship with all patients, introducing possible rater bias. However, use of a single rater to conduct consistent, standardized assessment eliminated discrepancies caused by multiple raters and represented the integrated assessment and treatment processes typically encountered in clinical practice.

The possible effects of comorbid Axis I and II disorders in the patients were not assessed in our analyses. Comorbid anxiety disorders may adversely affect depression treatment outcomes,[41] and the effect of personality disorders on the treatment of depressed patients is still debated.[42] Although there was no evidence that baseline illness severity differed between our treatment groups, we could not measure whether differences existed in the prevalence or severity of comorbid anxiety and personality disorders and whether comorbidities may have confounded our findings. We included patients with these comorbidities in order to enhance the generalizability of our findings, since comorbid Axis I[29] and Axis II disorders[30] are common in community outpatient samples.

Finally, SSRI discontinuation syndrome symptoms such as insomnia, fatigue, anxiety, and irritability can

mimic those of depression recurrence.[43] To reduce risk of the syndrome in the discontinuation group, we slowly tapered the SSRI dose over 2 to 5 months. Of the 21 subjects who relapsed in the discontinuation group, 3 relapsed in the first month following discontinuation and 2 relapsed in the second month. Despite our efforts, SSRI discontinuation syndrome cannot be definitively excluded in explaining patient relapse within the first few months after discontinuation and may have elevated our estimates of depression relapse risk associated with SSRI discontinuation. Nonetheless, SSRI discontinuation syndrome symptoms that emerge despite slow taper represent a difficult obstacle to discontinuation in clinical practice.

This study demonstrates that in a naturalistic clinical setting, relapse risk in MDD is high even after 5 years of stability on SSRI treatment, and subtle residual symptoms confer added risk. Extension of successful long-term SSRI maintenance beyond 5 years appears to provide clinically meaningful prophylactic benefit by markedly reducing subsequent relapse risk. Based on our findings, SSRI maintenance that is well tolerated and efficacious for 5 years should probably be continued for at least 2.5 additional years, the duration in which significant differences in relapse risk between continued and discontinued patients were demonstrated. Discontinuation should likely be avoided in patients with residual symptoms even after this period. If SSRI discontinuation is attempted, patients should be informed of their elevated relapse risk and monitored closely for relapse.

Drug names: citalopram (Celexa and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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