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ORIGINAL PAPER

Type of residual symptom and risk of relapse during the continuation/maintenance phase treatment of major depressive disorder with the selective serotonin reuptake inhibitor fluoxetine

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Abstract Relapse of major depressive disorder (MDD) is a common clinical problem. Identifying relapse predictors could lead to strategies that reduce relapse risk. This study is designed to determine whether residual symptoms predict relapse risk during the continuation/maintenance treatment of MDD. 570 MDD patients received open-label fluoxetine for 12 weeks. Under double blind conditions, 262 patients who responded by week 12 were randomly assigned to continue fluoxetine or switch to placebo for 52 weeks or until relapse. Residual symptoms were measured using the Symptom Checklist-90 and the Symptom Questionnaire. The relationship between residual symptom severity and relapse risk was assessed. Without adjusting for overall residual symptom severity, a greater severity of residual obsessive-compulsive and phobic anxiety symptoms predicted greater relapse risk. After adjusting for overall residual symptom severity, only severity of phobic anxiety symptoms predicted relapse risk. The predictive value of phobic anxiety symptoms with respect to relapse risk was independent of treatment assignment. The results indicated that there may be a specific pattern of residual symptoms associated with depressive relapse during antidepressant continuation/maintenance, which is unrelated to treatment assignment. Future studies are needed to further explore the relationship between residual symptoms and relapse risk in MDD. Clinical implications: (1) It is important to treat residual symptoms among antidepressant responders/remitters in order to decrease relapse risk. (2) Clinicians should target residual phobic anxiety symptoms in order to decrease relapse risk. (3) Clinicians should target residual obsessive-compulsive symptoms in order to decrease relapse risk. Limitations: (1) limited generalizability due to inclusion/exclusion criteria; (2) lack of active comparator treatment group; (3) post hoc analysis.

Keywords Depression · Unipolar · SSRI · Residual symptoms · Relapse

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Introduction

Major depressive disorder (MDD) is a prevalent illness that is frequently associated with significant disability, morbidity, and mortality. Results from the 2003 National Comorbidity Replication study found that the lifetime prevalence of MDD among American adults is 16.2%, ranking it among the most common and costly medical illnesses [1]. Despite the development and availability of numerous treatment options for MDD, studies have shown that antidepressant monotherapy yields only modest rates of response and remission. For example, in the multi-center Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, which involved a large, representative group of patients with MDD, monotherapy with the selective serotonin reuptake inhibitor (SSRI) citalopram produced remission rates of, roughly, 30% [2].

Furthermore, a significant proportion of patients who do experience remission following successful treatment with antidepressants will relapse, despite continued treatment [3]. Unfortunately, however, there is a paucity of information on the risk factors for depressive relapse/recurrence following response/remission in MDD.

A growing number of studies have focused on examining whether the degree of residual symptomatology following the acute-phase of treatment of depression can serve as a predictor of relapse or recurrence in major depression. In the first such study, Paykel and colleagues (1995) followed 60 patients for 12–15 months after remission. The authors found that 76% of patients who experienced residual symptoms after remission relapsed over the follow-up period as opposed to 25% of those without residual symptoms, suggesting that residual symptoms are strong predictors of subsequent short-term depressive relapse [4]. In an attempt to further explore the relationship between residual symptoms and longer-term recurrence, Kennedy and Paykel (2004) assessed this original study cohort of patients over a follow-up period of 8–10 years. They found that patients with residual symptoms reported a greater number of depressive symptoms, though not at full criteria for major depression, as well as impairments in social functioning over the follow-up period [5]. Judd and colleagues (1998) also examined the relationship between residual symptoms and subsequent rates of relapse by following patients that had recovered from their first lifetime major depressive episode naturalistically over a 10 to 12-year follow-up period. The authors found that the presence of residual sub-threshold depressive symptoms at recovery from a major depressive episode predicted poorer long-term outcome, characterized by shorter times to episode relapse/recurrence (including first relapse episode) as well as a greater number of relapses and recurrences, over the course of long term follow-up [6, 7]. Interestingly, Judd and colleagues observed a similar phenomenon among patients with bipolar disorder (type 1 or II): patients who experienced residual symptoms at recovery from a major affective episode relapsed into subsequent episodes more than 3 times as fast over a 17-year follow-up period as patients who were asymptomatic at recovery [8]. Finally, in a more recent study, Rush et al. (2006) reported that patients in the STAR*D study who were in remission were less likely to experience a subsequent depressive relapse than patients who had only responded to their treatments [9].

Taken together, the results from these studies demonstrate that residual symptoms at recovery are strong predictors of both short- and long-term relapse, the effects of which are seen not only in MDD but also in other affective disorders such as bipolar disorder. Relatively few studies, however, have focused on which specific residual symptoms weigh more heavily on subsequent risk of relapse. A study by Dombrovski and colleagues (2007) utilized data from a clinical trial of maintenance treatment of late-life depression to analyze the impact of overall residual symptom severity on depressive recurrence. Both residual anxiety and residual sleep disturbance were found to be significant independent predictors of early recurrence across treatment groups [10]. The encouraging results of Dombrovski's study highlight the need for more studies that define the specific depressive symptoms that are strong predictors of relapse. The purpose of the present study was to explore the impact of residual symptom type on risk of MDD relapse during the continuation/maintenance treatment with the SSRI fluoxetine among fluoxetine responders. In order to achieve this, we re-analyzed data from a 52-week, randomized, double-blind, placebo-controlled trial of fluoxetine continuation/maintenance treatment for MDD patients who had responded following a 12-week, open-label, flexible-dose trial of fluoxetine.

Methods

The present work is a post hoc analysis of data from a clinical trial of fluoxetine in MDD [11]. The original trial was primarily designed to identify whether a true versus placebo pattern of antidepressant response during the acute phase of treatment could predict long-term treatment outcome (i.e. relapse rates during the continuation and maintenance phases) [11]. However, a secondary goal of that study was to identify predictors of relapse during the continuation/maintenance phase of MDD.

For that trial, 627 patients, 18–65 years of age, with current MDD defined using DSM-IV criteria were recruited at one of two sites: either the New York State Psychiatric Institute in New York City ($n = 372$) or the Depression Clinical and Research Program of the Massachusetts General Hospital in Boston ($n = 254$). Institutional review boards at both sites approved the study, and all participants provided written informed consent. Diagnoses were made using the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-PE) [12] with no minimum score for severity of depressive symptoms required for inclusion in the study.

Medical screening was performed, including medical history, physical examination, ECG, CBC, blood chemistry profile, thyroid function tests, urinalysis, and urine drug screen. Patients were excluded from the study if they were at significant risk of suicide; were pregnant or breastfeeding, were women not using effective contraception; had an unstable physical disorder; had a lifetime history of any organic mental disorder, psychotic disorder, or mania; had a history of seizures; had a neurological

disorder that significantly affects central nervous system function; had met criteria for substance abuse or dependence in the previous 6 months, other than nicotine dependence; were taking medications that may cause or exacerbate depression; had clinical or laboratory evidence of hypothyroidism without adequate and stable replacement therapy; or had a history of non-response to an adequate trial of a selective serotonin reuptake inhibitor (SSRI) (defined as a 4-week trial of $\geq$40 mg of fluoxetine or the equivalent daily).

After a 1-week medication-free wash-out period, patients ($n = 570$) who continued to meet inclusion criteria and whose symptoms had not improved significantly (CGI-I score >2) began a 12-week course of open-label treatment with fluoxetine. Patients were evaluated by a research psychiatrist weekly during the first 6 weeks, biweekly for the next 4 weeks, and weekly for the final 2 weeks. Target fluoxetine dosages were 10 mg/day for the first week, 20 mg/day for weeks 2–4, 40 mg/day for weeks 4–8, and 60 mg/day for weeks 5–12. The dose was increased to meet the target only if the patient tolerated the medication well, and it was increased to 40 mg daily for all patients who could tolerate it. Treatment response during the acute phase was defined as a Clinical Global Impressions-Improvement (CGI-I) [13] scale score less than 3 for the last two visits of the open-label phase and no longer meeting DSM-IV criteria for MDD (by SCID-PE).

Patients who responded to the medication by week 12 ($n = 262$) entered a discontinuation phase during which they underwent random assignment, under double-blind conditions with computer-generated randomization, either to continue taking fluoxetine ($n = 131$) at the dose to which they had responded or to switch to placebo ($n = 131$) for 52 weeks or until relapse. Patients were seen monthly for the duration of the 52-week trial. By convention, the first 6 months of this period were considered the continuation phase, and the remainder, the maintenance phase. Identical fluoxetine or placebo capsules were dispensed by a research pharmacist. Compliance was monitored by counting returned capsules; participants whose adherence to the protocol was judged inadequate by the treating research psychiatrist were removed from the study. Relapse during the double-blind discontinuation phase was defined as having at least two consecutive weeks of ratings of less than "much improved" on the CGI improvement scale compared with ratings at entry into the study.

Residual symptom measures

The Symptom Questionnaire (SQ) [14] and the 90-item, self-report Hopkins Symptom Checklist (SCL-90) [15] administered during the randomization visit (baseline visit of the continuation and maintenance phase of the study) were used to assess residual symptoms.

Symptom Questionnaire items are scored as either yes or no, based on the presence/absence of each symptom. The SQ contains sub-scales, including depressed mood (D), anxiety (A), anger-hostility (H), and somatic symptoms (SS).

SCL-90 items are scored as 0 (symptom not present), 1 (a little bit), 2 (moderately), 3 (quite a bit), or 4 (extremely), based on the severity of each symptom. SCL-90 contains sub-scales, including somatic symptoms (SS), obsessive-compulsive symptoms (OC), interpersonal sensitivity (IPS), depressed mood (D), anxiety (A), hostility (H), phobic anxiety (PA), paranoid ideation (PI) and psychoticism (P).

Statistical tests

In order to test whether the presence of individual residual symptoms predicted an increased risk of MDD relapse, we conducted a survival analyses (Cox proportional hazards regression), using SPSS 16.0, with time to relapse as the dependent variable and the following independent variables: (1) gender, (2) chronicity (as defined in the McGrath et al. 2006 manuscript), (3) neurovegetative symptom pattern (as defined in the McGrath et al. 2006 manuscript), and (4) each individual SQ or SCL-90 subscale score during the randomization visit (week 12). Gender, chronicity, and neurovegetative pattern were added to the model since they were found to predict risk of relapse (not differential by treatment) in the original study [11].

There is often a correlation between the severity of individual symptoms and overall episode severity in MDD. Therefore, in order to test whether the presence of specific residual symptoms predicted an increased risk of MDD relapse that was independent of overall residual MDD symptom severity (i.e. the global severity of residual symptoms), we conducted a second set of survival analyses (Cox proportional hazards regression), with time to relapse as the dependent variable and the following independent variables (1) gender, (2) chronicity (as defined in the McGrath et al. 2006 manuscript), (3) neurovegetative symptom pattern (as defined in the McGrath et al. 2006 manuscript), (4) and 17-item Hamilton Depression Scale (HAM-D-17) [16] score during the randomization visit (week 12), and (5) each individual SQ or SCL-90 subscale score. This second set of survival analyses was limited to those items found significant in the first set of analyses.

Finally, a third cox regression model was constructed to examine whether any residual symptoms were predictive of differential relapse by treatment between patients maintained on either fluoxetine or placebo. Specifically, time to relapse was set as the dependent variable and the following

variables were set as independent variables: (1) HAM-D-17 score during the randomization visit (week 12); (2) each individual SQ or SCL-90 subscale score found to significantly predict relapse; (3) treatment assignment (fluoxetine or placebo); (4) the interaction between treatment assignment and SQ or SCL-90 sub-scale score, (5) gender, (6) chronicity, and (7) neurovegetative symptom pattern. This was done in order to examine whether SQ or SCL-90 subscale scores found to predict relapse were also differential predictors of relapse (i.e. to fluoxetine versus placebo). This third set of survival analyses was limited to those items found significant for overall prediction regardless of treatment assignment (i.e. the second set of analyses). Two-sided statistical tests were employed, with alpha set at the 0.05 level of significance.

Results

The results of the original study are reported elsewhere (McGrath et al. 2006). Briefly, the participants who underwent random assignment were a mean age of 38.2 years (SD = 10.9), and 55.3% were female. Their mean HAM-D score was 17.1 (SD = 4.1) at baseline and 4.9 (SD = 3.1) at randomization; 22.7% of them had a history of dysthymia and thus currently had "double depression." About two-thirds (35%) of the participants had one or more comorbid axis I disorder, most commonly panic disorder (13.3%), social phobia (12.4%), and alcohol dependence (10.6%) (percentages are nonexclusive). During this phase, 85 participants left the study, on average 16.4 weeks (SD = 2.0) after randomization; 34 of them were from the placebo group (26.0% of the placebo group), and 51 were from the fluoxetine group (38.9%). The most common reasons for leaving during this phase were removal for inadequate adherence (30.6% of those who left the study), loss to follow-up (14.1%), and side effects (7.1%). Fluoxetine treatment during continuation and maintenance treatment was associated with continued remission (ratio of relapse hazard during placebo substitution to relapse hazard during fluoxetine continuation = 1.73; 95% CI = 1.20–2.51). The relapse rates at the end of the continuation phase (6 months after randomization) were 35.2% for the fluoxetine group and 61.8% for the placebo group; after 1 year, they were 45.9% for the fluoxetine group and 72.0% for the placebo group. Table 1 presents the severity of residual symptoms measured by SCL-90 subscale scores and SQ subscale scores during the baseline visit of the double-blind phase.

Table 1 Residual symptom severity at baseline of continuation/maintenance phase (randomization visit)

Sub-scale	Mean score[a]	SD[a]	(Reference mean)[b]	(Reference SD)[c]
SQ-A	5.0	4.6	2.5	2.8
SQ-D	4.4	4.1	3.8	2.1
SQ-SS	3.2	3.7	4.4	1.1
SQ-H	3.1	4.3	3.9	3.8
SCL-SS	1.3	0.4	0.3	0.4
SCL-OC	1.7	0.6	0.3	0.4
SCL-IPS	1.6	0.6	0.2	0.3
SCL-D	1.8	0.7	0.3	0.4
SCL-A	1.4	0.5	0.3	0.3
SCL-H	1.3	0.4	0.3	0.4
SCL-PA	1.2	0.4	0.1	0.3
SCL-PI	1.4	0.6	0.3	0.4
SCL-P	1.3	0.4	0.1	0.2

SD standard deviation

[a] Residual symptom severity of MDD patients at randomization baseline

[b] For SCL: reference population of $n = 974$ non-patient adults from Derogatis LR (1994). SCL-90: administration, scoring, and procedures manual (3rd edition). Distributed by National Computer Systems, Inc. PO Box 1416. Minneapolis, MN 55440, USA

[c] For SQ: reference population of $n = 50$ normal subjects from Phillips KA, Siniscalchi JM, McElroy SL (2004) Depression, anxiety, anger, and somatic symptoms in patients with body dysmorphic disorder. Psychiatr Q 75(4):309–320

Individual symptom predictors (first set of survival analyses)

Results of the first set of survival analyses are presented in Table 2. A hazard ratio greater than 1 indicates a greater risk of relapse as residual symptom scores increase, while a hazard ratio less than 1 indicates a lesser risk of relapse as residual scores increase. Not adjusting for overall residual symptom severity (HAM-D-17 score), only SCL-OC (obsessive-compulsive, $P = 0.03$; hazard ratio = 1.55, indicating a 1.55-fold increase in the hazard of relapse for each one-point increase in SCL-OC residual symptom scores), and SCL-PA (phobic anxiety, $P = 0.001$; hazard ratio = 2.4, indicating a 2.4-fold increase in the risk of relapse for each one-point increase in SCL-PA residual symptom scores) were found to predict a greater risk of relapse.

Specific symptom prediction adjusted for overall severity of residual symptoms (second set of survival analyses)

Adjusting for overall residual symptom severity (HAM-D-17 score), SCL-OC was not found to significantly predict risk of relapse ($P = 0.09$; hazard ratio = 1.51). However, adjusting for overall residual symptom severity (HAM-D-17 score), SCL-PA remained significant ($P = 0.01$) with a

Table 2 SQ and SCL-90 sub-scale scores as predictors of relapse

Score	*P* value[a]	Hazard ratio[a]
SQ-A	0.78	1.00
SQ-D	0.09	1.04
SQ-SS	0.45	1.02
SQ-H	0.87	0.99
SCL-SS	0.38	1.24
SCL-OC	0.03	1.55
SCL-IPS	0.64	1.09
SCL-D	0.96	0.99
SCL-A	0.29	1.28
SCL-H	0.13	1.63
SCL-PA	0.001	2.40
SCL-PI	0.05	1.49
SCL-P	0.07	1.96

SQ items are scored as either yes or no, based on the presence/absence of each symptom. The SQ contains sub-scales, including *D* depression, *A* anxiety, *H* anger-hostility, and *SS* somatic symptoms

SCL-90 items are scored as 0 (symptom not present), 1 (a little bit), 2 (moderately), 3 (quite a bit), or 4 (extremely), based on the severity of each symptom. SCL-90 contains sub-scales, including *SS* somatic symptoms, *OC* obsessive-compulsive symptoms, *IPS* interpersonal sensitivity, *D* depression, *A* anxiety, *H* hostility, *PA* phobic anxiety, *PI* paranoid ideation and *P* psychoticism

A hazard ratio >1 implies a greater risk of relapse as residual symptom severity increases, while a hazard ratio <1 implies a lesser risk of relapse as residual symptom severity increases

[a] Not adjusting for overall residual symptom severity (HAM-D-17 scores)

hazard ratio of 2.24 (indicating a 2.24-fold increase in the risk of relapse for each increase in SCL-PA residual symptom scores).

Specific symptom prediction of relapse differential by treatment (third set of survival analyses)

Only one such analysis was conducted. Specifically, the interaction term (interaction between SCL-PA residual symptom score and assignment to fluoxetine versus placebo), when added to the model (from the second set of analyses), was not found to be statistically significant ($P = 0.66$; hazard ratio = 1.27), suggesting that the predictive value of SCL-PA scores with respect to risk of relapse was equivalent for the fluoxetine- and placebo-treatment arms.

Discussion

The present study is the first to test a variety of residual symptom types as predictors of relapse during the continuation and maintenance treatment of MDD with the SSRI fluoxetine or placebo. Of variety types of residual symptoms tested, a greater severity of two residual symptoms (obsessive-compulsive and phobic anxiety) were found to significantly predict a higher risk of relapse during continuation/maintenance phase treatment of MDD when not adjusting for overall residual symptom severity (as assessed by the 17-item Hamilton Depression Scale total score). After adjusting for overall residual symptom severity, only the severity of phobic anxiety symptoms was found to significantly predict risk of relapse. In fact, the predictive value of phobic anxiety scores with respect to risk of relapse was equivalent for the fluoxetine- and placebo- treatment arms. The hazard ratio of severity of residual phobic anxiety symptoms as a predictor of time to relapse, controlling for overall residual symptom severity, was 2.24, indicating a greater than twofold increase in the risk of depressive relapse for each increase in phobic anxiety symptom scores (with overall depression severity kept constant). Finally, a number of other types of residual symptoms, including somatic symptoms, general anxiety, and hostility were not found to significantly predict risk of relapse.

The residual phobic anxiety symptoms may predict a greater risk of MDD relapse that is independent of global residual symptom severity may have clinical implications. Given the considerable risk of relapse among antidepressant responders and remitters during long-term treatment, it would be useful to examine whether employing different pharmacologic interventions could lessen the risk of illness recurrence. Specifically, it would be interesting to study whether targeting residual phobic anxiety symptoms with the use of benzodiazepines, buspirone and other anxiolytic agents may serve to reduce risk of relapse of MDD. Unfortunately, however, to date, the only treatment strategy that has been consistently studied as a pharmacotherapeutic intervention in order to prevent MDD relapse is continuation/maintenance treatment with antidepressants at doses used in the acute phase of treatment. Therefore, the present findings, albeit preliminary, suggest that the predictive power of residual phobic anxiety symptoms be examined in other data sets, including those with medications other than fluoxetine, to examine whether this effect is replicated in other studies. If it were, this might warrant future studies examining the use of adjunctive treatment strategies targeting residual symptoms such as phobic anxiety in order to reduce the risk of MDD relapse/recurrence.

While the above findings are quite interesting, several limitations to this study need to be considered in interpreting the results. Clinical trials, including the present one, typically involve a number of inclusion and exclusion criteria, and it is therefore not possible to extend findings

from clinical trials to patient populations typically excluded form clinical trials (i.e. patients who are actively suicidal, with psychotic symptoms, with uncontrolled medical illness, or with bipolar disorder). In addition, although the present trial did not identify a robust relationship between a number of residual symptoms and time to depressive relapse, it may have been underpowered to identify weaker effects of such residual symptoms on long-term treatment outcome. Furthermore, due to the number of analyses performed, it is not possible to rule out whether some of our findings are due to chance alone. Therefore, the present results are, merely, preliminary/suggestive and need to be confirmed by future studies. Moreover, none of the SQ subscales was found to significant predict risk of relapse, suggesting that, perhaps, the SQ may not be sensitive enough as a scale when used to measure the severity of residual symptoms in MDD (in fact, in Table 1, it appears that mean SQ scores for our sample and a reference population of non-depressed adults were, roughly, equivalent). Finally, the present study did not employ a second, "active" treatment arm. It would have been interesting to explore whether or not a similar relationship between specific residual symptom types and risk of relapse would also hold for antidepressants that employ a different mechanism of action.

In conclusion, the results of the present study suggest there may be a specific pattern of residual symptoms associated with depressive relapse during antidepressant continuation/maintenance but this is not related to treatment. Future studies are needed to replicate and further explore the relationship between residual symptoms and relapse in MDD.

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