Published in final edited form as:
Compr Psychiatry. 2011 ; 52(2): 151–155. doi:10.1016/j.comppsych.2010.05.004.

Examining the Role of Race and Ethnicity in Relapse Rates of Major Depressive Disorder

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Abstract

Objective—We test the hypothesis that racial or ethnic differences exist in relapse rates to fluoxetine discontinuation in Major Depressive Disorder (MDD).

Method—Data are from a prospective study examining the relapse rates secondary to fluoxetine discontinuation in MDD. Subjects in the discontinuation phase consisted of 255 adults aged 18 to 65, 214 subjects who self-identified as Caucasian, 22 as African American, 13 as Latino American, and six as Asian American.

Results—In both the fluoxetine and placebo groups, no statistically significant differences emerged when comparing time to relapse for minority groups as compared to the Caucasian population. Adjusting for statistically significant predictors of relapse (symptom severity, neurovegetative symptom pattern, gender) and for educational level did not change the outcome of the survival analyses.

Conclusions—Although the size of minority groups in this sample was modest, in a randomized, controlled trial setting, minority and Caucasian patients may have similar rates of relapse in MDD. This finding reinforces the importance of maintenance treatment in relapse for both minority as well as Caucasian patients with MDD. Given the self-selecting nature of clinical trials, future studies are needed to further examine the potential influence of underlying cultural factors on clinical outcomes in minority populations.

Keywords

Major Depression; Minority populations; Relapse

Introduction

With the Surgeon General's Report on mental health in 2001, there has been growing interest in improving mental health treatment of minorities, who have been shown to not receive the same quality of care as Caucasians (1). Moreover, the prevalence rate of antidepressant use among depressed minorities has been found to range from 8.7% to

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17.4%, compared with the prevalence rate of 41.3% among Caucasians (2). Factors complicating treatment for these groups include barriers in language between providers and patients, limited access to health care, as well as under-recognition of, and greater perceived stigma towards mental illness (1,3,4,5,[6],7,8,9,10).

Researchers have also postulated that race and ethnicity may also play a role in response to pharmacological treatment because of potential differences in pharmacologic factors including pharmacokinetics and pharmacodynamics, although the data have been mixed. In a systematic literature review exploring how minority groups may differ in their response to antidepressant medication, African Americans as a group were found to metabolize medications for mood and anxiety disorders at a slower rate, suggesting that lower starting doses and slower titration of medication may be needed for African Americans (11). Similarly, in the STAR*D study, an effectiveness trial of antidepressant treatment in primary and specialty care settings, Lesser et al. also sought to analyze differences between ethnic groups (12). Their analysis revealed that Black and Hispanic groups' remission rates on citalopram were lower than Caucasians' rates, as measured by the Hamilton Rating Scale for Depression (HAM-D) and the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR). However, after controlling for education and income, remission rates were no longer statistically different between Blacks, Hispanics, and Caucasians on the HRSD. This might suggest that differences in response rates were not primarily pharmacologic, but might be related to attitudes toward illness and treatment influenced by social aspects of minority status. Similar findings regarding minority response rates to antidepressant medication have been found in randomized, placebo-controlled trials. In a pooled analysis of seven, double-blind placebo-controlled clinical trials of duloxetine, there was no evidence that African Americans differed in their response to duloxetine as compared to Caucasians (13). In a larger pooled analysis using 104 double-blind, placebo-controlled clinical trials of paroxetine, little difference was found in the response or tolerability profiles between ethnic groups (14).

While limited and conflicting evidence exists regarding minority response rates to antidepressant treatment, even less is known about minority relapse rates in Major Depressive Disorder (MDD). In this study, we investigate the relapse rates among minority patients with MDD using data from a prospective study examining the relapse rates secondary to fluoxetine discontinuation in MDD (15). We test the hypothesis that racial and ethnic differences exist in relapse rates either during continued fluoxetine treatment or following fluoxetine discontinuation in MDD. If ethnic differences exist, we further explore if this difference is attributable to demographic factors such as socioeconomic status, measured by employment and education level, as suggested by the STAR*D study (12). To our knowledge, this is the first analysis to address racial and ethnic differences in relapse rates of patients with MDD after they have responded to pharmacological treatment.

Methods

This data analysis represents a secondary analysis of an original study by McGrath et al. (2006). In the original study, a total of 627 patients 18 to 65 years of age who met DSM-IV criteria for a current episode of MDD were recruited by research programs at the New York State Psychiatric Institute in New York City and the Depression Clinical and Research Program of the Massachusetts General Hospital in Boston. The study was approved by institutional review boards at both sites, and all participants provided written informed consent. Diagnoses were established using the Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition. No minimum score for severity of depressive symptoms was required for inclusion in the study. Patients were allowed to enter the study if psychotherapy was initiated more than one month prior to the screen visit. Baseline medical

screening included 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 CNS function; had been active substance abusers or had substance dependence in the previous six 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 (defined as a four-week trial of ≥ 40 mg of fluoxetine or the equivalent daily).

After a 1-week medication-free wash-out, patients who continued to meet inclusion criteria and whose symptoms had not improved significantly began a 12-week course of open-label treatment with fluoxetine. They were seen weekly by a research psychiatrist during the first 6 weeks, biweekly for the next 4 weeks, and weekly for the remaining 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 was rated on the 17-item Hamilton Depression Scale (HAM-D-17) and the Clinical Global Impressions Severity and Improvement Scales (CGI-S and CGI-I).

Patients who responded to the medication by week 12 entered a discontinuation phase during which they underwent random assignment under double-blind conditions with computer-generated randomization, either to continue taking fluoxetine at the dose to which they had responded or to take placebo for 52 weeks or until relapse. 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, who was masked to clinical features of the patient's treatment. Adherence 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. In the continuation and maintenance phases, patients were seen biweekly during the first two months, and monthly for the remaining 10 months of the study. The clinician-rated CGI-I was assessed at each visit in the continuation and maintenance phases. As defined previously, relapse during the double-blind discontinuation phase was defined as having at least 2 consecutive weeks of ratings of less than "much improved" on the CGI-I scale compared with ratings at entry into the study (15).

Data Analysis

The analysis was based on modeling the time to relapse using survival analysis by using Cox Proportional Hazards Regression model (16). The inferences are based on a survival analysis as a function of treatment (fluoxetine or placebo). Potential demographic predictors of relapse, age, gender, years of education, and marital status, were identified using logistic regression, and the survival curves were adjusted for the identified predictors as covariates. In addition, survival curves were adjusted for gender, chronicity, neurovegetative symptom pattern, and symptom severity (as measured by the HAM-D 17), which were found to be predictors of relapse in the main study analyses. Chronicity was rated on a 6-point scale (1=single episode; 2=mainly well, with recurrent episodes; 3=chronic, with multiple remissions; 4=chronic, with no more than two remissions; 5=chronic, intermittent; 6=chronic, persistent). Positive neurovegetative symptom pattern was found if a patient's

HAM-D 17 score using the typical positive symptoms such as insomnia and weight loss was at least equal to his or her score using the negative symptoms of these items, hypersomnia and weight gain. The symptom pattern was considered negative if the score was not at least equal (15). All reported statistical tests are two-tailed. All analyses were conducted using SPSS software (17).

Results

The demographics of the open-label phase of the study have been described in detail by McGrath et al, and are summarized in Table 1 (15). For phase two of the study, 292 participants were eligible and 30 elected not to continue in the study. Of the remaining 262 participants, 131 each were randomly assigned to the fluoxetine and placebo groups. The participants who underwent random assignment were a mean age of 38.2 years (SD = 10.9), 55.3% were female, 18.3% were married, and they had a mean of 15.1 years of education (SD = 2.5).

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%) (Chi-square=4.5, df=1, p=0.035). 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%). Vigorous efforts were made to ensure that all dropouts were contacted and interviewed. If worsening of symptoms was one of the reasons a participant left the study, that patient was not counted as a dropout. Chronicity, neurovegetative symptom pattern, symptom severity, and participation in psychotherapy across groups were not statistically significantly different (Table 1).

In phase two, 214 subjects self-identified as Caucasian, 22 as African American, 13 as Latino American, and 6 as Asian American. The groups were equivalent in age, female gender, and marital status (Table 2). To examine the hypothesis that there are ethnic differences predictive of time to relapse, a survival model was constructed for each treatment group, adjusting for predictors of relapse (chronicity, symptom severity, and neurovegetative symptom pattern). In both the fluoxetine and placebo groups, no statistically significant differences emerged when comparing time to relapse for minority groups as compared to the Caucasian population.

To adjust for potential demographic confounders, possible demographic predictors for relapse were tested using logistic regression from a list of potential variables (age, educational level, employment status, and marital status). In this analysis, only educational level (p= 0.023) emerged as statistically significant predictors of relapse. Adjusting for educational level in the survival model did not change the outcome; no statistically significant difference emerged when comparing time to relapse for minority groups as compared to the Caucasian population.

The time to relapse rates between treatment and placebo groups were compared by ethnic group using Cox Proportional Hazards Regression. Although only the Caucasian group showed a statistically significant difference between relapse rates of treatment versus placebo groups (p=0.001), in all minority groups, the same trend emerged of time to relapse being shorter for placebo groups versus treatment. Percentages of those relapsed overall, in the fluoxetine, and in the placebo groups by ethnic group are listed in Table 2.

Discussion

Although much has been written about the potential difference in response to antidepressants by racial and ethnic groups, little is known about relapse rates once antidepressants are discontinued. In this prospective study, we were unable to demonstrate a difference in relapse rates by race and ethnicity. Controlling for the role of predictors for relapse or potential demographic confounders did not change this outcome. In addition, that the placebo groups uniformly did worse as compared to the treatment groups highlights the importance of maintenance treatment of MDD, regardless of racial and ethnic background.

That racial and ethnic differences in relapse rates may not exist is an important finding, suggesting that providing minorities with the same close follow-up and resources as the mainstream population for treatment of MDD may yield similar outcomes. In this prospective, randomized controlled trial, research staff were able to closely monitor study patients, provide frequent structured follow-up visits and telephone reminders, and often offer remuneration for travel expenses. This is far from a “real world” scenario in which differences in access to care, rates of misdiagnosis, psychosocial stressors, or willingness to engage in treatment may play significant roles (18,19). Participants in clinical research have been found to be better educated than patients in many clinical settings, and are almost by definition more motivated for treatment and burdened by fewer co-morbidities, since many co-morbid conditions are exclusionary for clinical trials (20,21).

Other studies have suggested that ethnic and racial differences may not exist in the treatment of MDD. In the Partners in Care study, a randomized control trial, evidence-based care for depression was equally effective in reducing depressive disorders for minority and nonminority patients (22). In the IMPACT (Improving Mood-Promoting Access to Collaborative Treatment) study, similar rates of response to collaborative treatment for depression in minority and Caucasian patients were found (23). Finally, in a “real world” clinical trial, STAR*D, after adjusting for baseline clinical, demographic, and socioeconomic differences, the authors found similar remission rates among ethnic minority groups, although here too the population might be more motivated and better informed than might be found in many clinical settings (12).

Because this report constitutes a secondary analysis of data from the original study, it was not designed to specifically address the association of race and ethnicity and relapse. The numbers of minority patients are modest as compared to the mainstream Caucasian population, and represent a limitation of the study. One possibility is that these findings simply resulted from a type II error, in which a true difference went undetected because of random error or insufficient statistical power. The minority groups are small in size and minority status was determined by self-report. A genetic study has shown that self-reported ethnicity can be significantly discrepant with ethnicity determined by a panel of genetic markers, making self-report potentially less accurate if one were concerned with genetic diversity in populations (24). However, except for the Asian American group, which was much smaller than the other minority groups, the proportions of those relapsed in the fluoxetine, placebo and overall groups were roughly similar by ethnic group (Table 2). In addition, a similar pattern of shorter time to relapse for placebo groups as compared to fluoxetine emerged by ethnic group, suggesting similar patterns of relapse overall in the minority and Caucasian groups.

In addition, there is likely substantial heterogeneity in each of the ethnic groups studied, and simple ethnic or racial identification may not capture well the diversity within each ethnic group, in terms of differences in language, acculturation, or cultural beliefs around illness or treatment. Research subjects are a motivated, self-selected group seeking voluntarily

psychiatric and pharmacological treatment, which may not be the case for minority patients in general. In non-clinical trial, naturalistic settings, many minority patients may be reluctant to seek mental health treatment for a variety of reasons, including perceived stigma associated with mental health treatment (25), a history of negative mental health treatment experiences (26), or perceptions that antidepressants are not acceptable treatments for depression (27). This study did not probe into subjects' cultural or ethnic background, language, level of acculturation, attitudes towards mental health, or illness belief systems, all which may impact treatment outcome. Future studies focusing on larger groups of minorities should address these issues, as they may shed light upon differences in outcome or lack thereof in minorities as compared to Caucasian patients with MDD.

In a randomized, controlled trial setting, minority and Caucasian patients appear to have similar rates of relapse in MDD, whether on fluoxetine or placebo, and adjusting for sociodemographic variables appears not to change this outcome. This finding reinforces the importance of maintenance treatment in relapse for both minority as well as Caucasian patients with MDD.

Future studies enriched with minority populations are needed to further explore the course of treatment and relapse in MDD. The study design should address the potential influence of cultural factors on differences in clinical outcomes for minority populations. Although racial and ethnic disparities may exist in mental health for minorities, understanding the underlying mechanisms responsible for such disparities is paramount. As the limitations of our analysis suggest, moving beyond the examination of simple racial, ethnic, and sociodemographic variables towards a deeper understanding of cultural factors influencing relapse will ultimately improve treatment for all patients with MDD.

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Table 1

Sociodemographic Measures and Clinical Characteristics for Open-Label Phase I by Racial/Ethnic Group

Measure	Caucasian (n= 469)	African American (n= 66)	Latino American (n=58)	Asian American (n=18)
Age, mean (SD)	38.60 (11.5)	32.58 (10.6)	35.19 (10.6)	30.67 (8.6)
Female Gender, n (%)	248 (52.9)	41 (62.1)	33 (56.9)	11 (61.1)
Education (yr), mean (SD)	14.91 (2.6)	13.50 (2.2)	13.98 (2.6)	15.11 (2.1)
Employment Status, n (%)				
-Employed full-time	231 (49.3)	31 (47.0)	19 (32.8)	4 (22.2)
-Employed part-time	74 (15.8)	10 (15.2)	8 (13.8)	4 (22.2)
-Unemployed	103 (22.0)	16 (24.2)	19 (32.8)	3 (16.7)
Marital Status, n (%)				
-Never married	272 (58.0)	43 (65.2)	35 (60.3)	12 (66.7)
-Married	97 (20.7)	6 (9.1)	4 (6.9)	2 (11.1)
-Separated/divorced	97 (20.7)	17 (25.8)	15 (25.9)	4 (22.2)
-Widowed	3 (0.6)	0 (0)	3 (5.2)	0 (0)
Clinical Characteristics				
Chronicity, mean (SD)	3.95 (1.72)	4.43 (1.6)	4.15 (1.5)	4.38 (1.6)
Negative neurovegetative pattern, n (%)	109 (23.2)	10 (15.2)	4 (6.9)	5 (27.8)
Positive neurovegetative pattern, n (%)	190 (40.5)	25 (37.9)	20 (34.5)	2 (11.1)
Symptom severity, mean (SD)	7.10 (5.5)	7.68 (6.4)	8.30 (5.1)	6.71 (7.4)
Receiving psychotherapy, n (%)	49 (10.4)	8 (12.1)	5 (8.6)	2 (11.1)

Table 2

Sociodemographic Measures and Percentage Relapsed for Phase II by Racial/Ethnic Group

Measure	Caucasian (n= 214)	African American (n= 22)	Latino American (n=13)	Asian American (n=6)
Age, mean (SD)	38.91 (10.9)	33.73 (9.9)	37.46 (10.4)	33.33 (12.5)
Female Gender, n (%)	121 (56.6)	14 (63.6)	5 (38.5)	4 (66.7)
Education (yr), mean (SD)	15.26 (2.6)	14.59 (2.1)	14.31 (2.6)	14.5 (2.9)
Employment Status, n (%)				
-employed full-time	121 (56.5)	12 (54.5)	6 (46.2)	2 (33.3)
-employed part-time	36 (16.8)	4 (18.2)	2 (15.4)	1 (16.7)
-unemployed	41 (19.2)	3 (13.6)	4 (30.8)	1 (16.7)
Marital Status				
-never married	121 (56.5)	15 (68.2)	7 (53.8)	5 (83.3)
-married	50 (23.4)	4 (18.2)	1 (7.7)	0 (0)
-separated/divorced	43 (20.1)	3 (13.6)	4 (30.8)	1 (16.7)
-widowed	0 (0)	0 (0)	1 (7.7)	0 (0)
Percentage relapsed, n (%)				
-overall, fluoxetine or placebo group n (% of total n)	99 (46.3)	10 (45.5)	5 (38.5)	5 (80.3)
-fluoxetine group, n (% of fluoxetine group)	35 (34.3)	6 (46.2)	1 (20.0)	2 (66.7)
-placebo group, n (% of placebo group)	64 (59.8)	4 (57.1)	4 (57.1)	3 (100)