Published in final edited form as:
Int J Geriatr Psychiatry. 2007 November ; 22(11): 1141–1146. doi:10.1002/gps.1804.

Predicting 6-week treatment response to escitalopram pharmacotherapy in late-life major depressive disorder

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SUMMARY

Objective—Approximately half of older patients treated for major depressive disorder (MDD) do not achieve symptomatic remission and functional recovery with first-line pharmacotherapy. This study aims to characterize sociodemographic, clinical, and neuropsychologic correlates of full, partial, and non-response to escitalopram monotherapy of unipolar MDD in later life.

Methods—One hundred and seventy-five patients aged 60 and older were assessed at baseline on demographic variables, depression severity, hopelessness, anxiety, cognitive functioning, co-existing medical illness burden, social support, and quality of life (disability). Subjects received 10 mg/d of open-label escitalopram and were divided into full (n =55; 31%), partial (n =75; 42.9%), and non-responder (n =45; 25.7%) groups based on Hamilton depression scores at week 6. Univariate followed by multivariate analyses tested for differences between the three groups.

Results—Non-responders to treatment were found to be more severely depressed and anxious at baseline than both full and partial responders, more disabled, and with lower self-esteem than full responders. In general partial responders resembled full responders more than they resembled non-responders. In multivariate models, more severe anxiety symptoms (both psychological and somatic) and lower self-esteem predicted worse response status at 6 weeks.

Conclusion—Among treatment-seeking elderly persons with MDD, higher anxiety symptoms and lower self-esteem predict poorer response after six weeks of escitalopram treatment.

Keywords

major depression; old age; escitalopram; treatment response

INTRODUCTION

About 50% of older patients treated for major depression do not achieve symptomatic remission and functional recovery with first-line pharmacotherapy (Little *et al.*, 1998;

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Thomas *et al.*, 2002). Moreover, the presence of residual depressive symptoms increases the risk for later relapse (Fava *et al.*, 1996; Sackeim *et al.*, 2001; Cuffel *et al.*, 2003; Karp *et al.*, 2004).

A recent primary care study showed that older patients suffering from severe depression, hopelessness, anxiety and limitations in physical functioning at baseline were less likely to respond fully to medication (Bruce *et al.*, 2004). In addition, cognitive impairment, especially executive dysfunction (Alexopoulos *et al.*, 2000), comorbid anxiety (Mulsant *et al.*, 1996; Lenze *et al.*, 2002; Alexopoulos *et al.*, 2005; Andreescu *et al.*, in press), low self-esteem (Gildengers *et al.*, 2005), lower social support and adverse life events (Dew *et al.*, 1997), and residence in low-income communities (Cohen *et al.*, 2006) have all been cited as predictors of delayed or partial treatment response. This study builds upon these findings in order to identify predictors of partial and non-response to initial 6-week pharmacotherapy of major depression in old age. We hypothesized that partial responders would be characterized by greater severity of depression, disability and cognitive impairment, higher rates of hopelessness and suicidal ideation, lower self-esteem and social support, and higher rates of comorbid anxiety disorders and symptoms compared to full responders. Although we had no *a priori* hypotheses about predictors of non-response (because the parent study is seeking specifically to test the efficacy of combination treatment for the large numbers of partially responding patients in clinical practice), we also chose to present predictors of non-response at 6 weeks, in an exploratory way, because of the relevance of doing so to clinical decision making and because we wished to explore whether partial responders resemble either full or non-responders more closely in their sociodemographic and clinical characteristics.

MATERIALS AND METHODS

Subjects

Between 1 June 2004 and 1 May 2006, we recruited 175 subjects aged 60 and above from primary care practices, and from our specialty mental health clinic for elderly people with mood and anxiety disorders. All subjects were currently experiencing a non-psychotic, unipolar major depressive episode, as established by the Structured Clinical Interview for DSM-IV, had a baseline rating of 15 or higher on the 17-item Hamilton Rating Scale for Depression (Hamilton, 1967), and scored at least 17 on the Folstein Mini-Mental Status Examination (Folstein *et al.*, 1975). Participants were excluded if they had a lifetime diagnosis of bipolar disorder, schizophrenia, schizoaffective or other psychotic disorders; dementia; a history of alcohol/ drug abuse within the past 12 months; or a history of non-response or non-tolerance to escitalopram. The study was approved by the University of Pittsburgh Institutional Review Board, and all subjects provided written informed consent.

Assessment

Pre-treatment assessments encompassed depression severity (Hamilton Rating Scale for Depression, HRSD-17; Hamilton, 1967), suicidal ideation (HRSD-17 item 3) hopelessness (Beck Hopelessness Scale; Beck *et al.*, 1974), anxiety severity (Hamilton Rating Scale for Anxiety; Hamilton, 1959), cognitive functioning (Mattis, 1988), co-existing medical illness burden (Cumulative Illness Rating Scale for Geriatrics, CIRS-G; Miller *et al.*, 1992), disability and health-related quality of life (Quality of Well-Being Scale, Bush *et al.*, 1982; MOS-Short Form; Ware and Sherbourne, 1992), and social support/self-esteem (Interpersonal Support Evaluation List, ISEL; Cohen *et al.*, 1985).

Subjects were seen once a week for 6 weeks by study clinicians (masters-level psychiatric nurses and PhD clinical psychologists) under the supervision of the medical director (MDM) and principal investigator (CFR). Vital signs, HRSD-17 scores, and suicidal ideation were

assessed during these sessions. At the end of 6 weeks, independent assessors administered the HRSD and classified participants as 'full responders' (HRSD ≤10) 'partial responders', (HRSD 11–14) and as 'non-responders' (HRSD ≥15). Criteria for level of response had been specified *a priori*. Twenty subjects were terminated from the study before week 6: eight due to medication side effects, eight due to consent withdrawal (respondent burden or preferences for other treatment), and four due to protocol non-compliance. All of these subjects started treatment and were therefore part of the intent-to-treat sample; their response was determined using the last observed value of the Hamilton Rating Scale for Depression.

Intervention

Subjects were openly treated with 6 weeks of escitalopram at 10 mg/day and supportive clinical management focusing on depressive symptoms (including suicidal ideation), medication side effects, sleep hygiene, and treatment adherence, but not incorporating any depression-specific psychotherapy. (Increases to 20 mg are allowed after 6 weeks in the case of partial or non-responders.) All psychotropic and over-the-counter medications were tapered over 1–2 weeks concurrent with the start of escitalopram pharmacotherapy. Participants unable to completely discontinue benzodiazepine therapy were converted to an equivalent dose of lorazepam.

Analysis

We hypothesized that partial responders to escitalopram monotherapy would be characterized by greater deverity of depression and anxiety, disability and cognitive impairment, higher rates of hopelessness and suicidal ideation, and more impaired social support and self-esteem compared to full responders. To test this hypothesis, depression severity, hopelessness, anxiety symptoms and disorders, cognitive status, health status, social support and health-related quality of life were compared using χ^2 analysis for categorical data and analysis of variance for continuous data. When a significant difference was detected, post-hoc comparisons were performed using the Tukey pairwise test. We also hypothesized that the baseline variables which differed across groups could be used to predict response status at 6 weeks. To test this hypothesis, we performed heirarchial polytomous logistic regression analysis (Stokes *et al.*, 1995) using demographic variables at the first step (sex, race, Hollingshead SES) and clinical variables at the second level (initiation/preservation, self esteem, medical burden, symptom severity of depression and anxiety). Since depression and anxiety symptom scores were highly correlated (r =0.66), we recomputed the depression score by subtracting out the anxiety items (9, 10, 11, 15) and recomputed the anxiety score by taking out the depression item (6). The response variable was treated as an ordinal variable: 0 =no response; 1 =partial response; 2 =full response. A two-tailed α =0.05 was used to determine statistical significance.

RESULTS

Fifty-five subjects (31%) were classified as full responders; 75 (42.9%) as partial; and 45 (25.7%) non-responders. Of the full responders, half (n =28, or 16% of the study group) were remitters (HRSD ≤6). Race was the only demographic characteristic that differed significantly (χ^2 =10.99, p =0.004) between partial and non-responders, with 85% (n =47) of full responders, 93% (n =70) of partial responders, and 71% (n =32) of non-responders self-identified as white (Table 1). The remaining 29% (n =13) of non-responders all self-identified as African-American. Socioeconomic status, as estimated by the Hollingshead Index of Socioeconomic Status, was evaluated in 163 of the 175 participants, and no significant difference between the three groups was detected. African-American participants did not differ in terms of severity of depression or anxiety, social support, or past history of

substance use when compared to white participants. However, African-Americans reported missing significantly more doses of escitalopram as compared to white participants: 35% *vs* 8% were non-adherent (χ^2 =14.79, p =0.0001), with adherence defined as having at least 80% of visits with no missed dosages reported.

Clinically, severity of depression and anxiety symptoms, hopelessness, health-related quality of life (disability), and social support differed across the three groups (Table 2). Partial responders reported higher levels of hopelessness than full responders, full responders reported more social support and better health-related quality of life than non-responders. Additionally, both full and partial responders had less severe depressive and anxiety symptoms at baseline compared to non-responders. Co-existing medical burden (CIRS-G), duration of index depressive episode, age of lifetime onset, percent with recurrent depression, suicidal ideation, and cognitive function (including executive impairment as measured by the Initiation/Perseveration subscale of the Mattis Dementia Rating Scale) did not differ across the three groups. Rates of pre-treatment benzodiazepine usage were 44% in nonresponders, 35% in partial responders, and 20% in full responders (χ^2_2=7.00, p =0.03).

Self-esteem was most impaired in non-responders and was the only contributor to the differences in social support (ISEL) between full and non-responders (F =4.51, df =2,169 p =0.012). Self-appraised social support, belonging, and tangible support did not differ. Full and partial responders had lower psychological and somatic anxiety subscores of the Hamilton Anxiety Scale (F =6.36, df =2,172 p =0.002 for psychological subscore; F =5.77, df =2,172 p =0.004 for somatic subscore). However, the groups did not differ in rates of any coexisting anxiety disorder (on the SCID for DSM-IV), including generalized anxiety disorder, or substance use.

Multivariate analysis

In order to determine which variables predicted treatment response, we performed a hierarchical polytomous logistic regression. There was no effect of demographic variables (including race) on response in the first step (Likelihood-rated (LR) test χ^2_3=2.36, p =0.50). The addition of clinical variables was highly significant (LR χ^2_6=19.23, p <0.005): self esteem (Wald χ^2 =5.07, p =0.024, Odds Ratio [OR] =0.89 [0.79, 0.98]) and severity of anxiety symptoms (χ^2 =5.14, p =0.023, OR =1.09 [1.01,1.18]) were retained as reliable predictors in the model. Predicted versus observed response was concordant in 65% of cases, discordant in 34% and tied in 1%. Race and self-reported medication adherence were not significant predictors in the multivariate analysis.

DISCUSSION

Our data show that older subjects with MDD who do not respond to a 6-week trial of escitalopram monotherapy can be characterized at baseline as more severely anxious as well as burdened with lower self-esteem compared to subjects who are either partial or full responders. Other studies from our center using data from different subjects have also shown that greater anxiety symptoms and lower self-esteem predict poor treatment response (Lenze *et al.*, 2002; Gildengers *et al.*, 2005). The finding of an association between lack of full response and higher anxiety scores is also consistent with previous literature (e.g. Flint and Rifat, 1997; Steffens and McQuoid, 2005). This information can be used by physicians to initially identify patients who may not respond quickly or completely to antidepressant monotherapy. There are implications for long-term outcomes, as well, because rapid, mixed, or delayed treatment response trajectories indicate which maintenance therapies are most effective (Dew *et al.*, 2001; Whyte *et al.*, 2004).

It should be noted that our initial hypothesis specified the profile of partial responders and that we had no a priori hypothesis about the profile of non-responders. Our data suggest that partial responders at 6-weeks resemble more closely full responders rather than they do non-responders. This is consistent with our recent observation, based upon an independent sample, that the majority of partial responders at 6 weeks of pharmacotherapy will become full responders by 12 weeks if patients 'stay the course', i.e. no change in treatment strategy is necessary (Mulsant *et al.*, 2006).

While race was not retained in the final multivariate prediction, we observed that 29% of non-responders were African-American. Some research has suggested that African-Americans could be expected to respond more quickly to SSRIs than whites due to higher prevalence rates of the L allele of the SERT polymorphism (Lotrich *et al.*, 2001; Lotrich *et al.*, 2003). Additionally, contrary to the results reported by Cohen *et al.* (2006), socioeconomic status did not predict response. Thus, the disparity in response to medication seen in African-Americans may therefore be due to cultural rather than biological or socioeconomic factors. Our observation that a significant number of African-American patients reported missing a dose of medication during the 6-week study period is consistent with other studies suggesting that African Americans may be less likely to accept antidepressant medication treatment (Cooper *et al.*, 2003).

Several limitations to this study exist. It is an open trial (i.e. the initial step of a treatment algorithm), not placebo-controlled. It may be the case that a 6-week trial of medication at a fixed dose is not enough time to clearly delineate between full and partial responders to treatment and that a longer trial may be necessary to fully determine response variability (Mulsant *et al.*, 2006).

In summary, this study suggests that non-responders to six weeks of escitalopram monotherapy are characterized by high levels of anxiety and low self-esteem at baseline. Additionally, partial and full responders to therapy were more alike than we originally believed. Understanding predictors of response to initial pharmacotherapy can enable both physicians and their patients to develop realistic management plans and goals for full recovery.

Acknowledgments

Supported in part by P30 MH071944; R01 MH37869, R01 MH43832, EXPORT P60 MD-000-207, T32 MH19986, and the University of Pittsburgh Medical Center (UPMC) endowment in geriatric psychiatry.

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KEY POINTS

- In elderly people with major depression, more severe anxiety symptoms (psychological and somatic) and lower self-esteem predict worse response status at six weeks of pharmacotherapy with escitalopram 10mg/day.
- A significantly greater proportion of non-responders were African-Americans; these subjects reported missing more doses of medication than European-American participants.

Table 1

Baseline demographic characteristics of study participants

	Full responders (*n* =55)	Partial Responders (*n* =75)	Non Responders (*n* =45)	*F* or X^2	df[1]	*p*
Age	73.6 (7.8)	72.2 (7.9)	73.7 (7.8)	0.77	172	0.47
%Women (n)	73% (40)	65% (49)	73% (33)	1.20	2	0.55
%Caucasian (n)	85% (47)	93% (70)	71% (32)	10.99	2	0.004[3]
Education, yrs	13.5 (3.2)	13.6 (2.6)	12.8 (2.3)	1.39	168	0.25
Hollingshead Index of Socioeconomic Status	43.6 (16.8)	45.2 (15.3)	42.1 (15.3)	0.51	160	0.60

[1] Denominator degrees of freedom for *F* ratios, numerator df =2.

[2] Natural log transformation prior to statistical comparison.

[3] Post-hoc: Partial responders differ from non responders.

Table 2

Baseline clinical and neuropsychological characteristics of study participants

	Full responders (*n* =55)	Partial Responders (*n* =75)	Non Responders (*n* =45)	*F* or X^2	df[1]	*p*
Duration of Index Episode median[2] (weeks)	41	66	55	0.63	70	0.53
Age of onset (years)	60.9 (18.2)	55.8 (21.2)	54.3 (19.5)	1.61	172	0.20
%Recurrent (n)	42% (23)	43% (32)	58% (26)	3.23	2	0.20
%Suicide ideation (HRSD item #3)	4% (2)	15% (11)	12% (5)	4.20	2	0.12
Beck Hopelessness Score	5.0 (4.5)	8.2 (5.3)	6.9 (5.1)	6.33	169	0.002[a]
Mattis Dementia Rating Scale – scaled score	8.5 (2.5)	9.1 (2.9)	8.9 (3.0)	0.71	168	0.49
Hamilton Rating Scale for Depression	18.1 (2.8)	18.5 (2.9)	20.2 (3.6)	6.72	172	0.002[b]
Hamilton Rating Scale for Anxiety	16.7 (4.5)	17.6 (4.2)	20.6 (6.0)	8.92	172	0.001[b]
Cumulative Illness Rating Scale total	10.1 (3.8)	10.5 (4.1)	9.9 (3.9)	0.32	172	0.73
MOS – Physical component subscore	44.9 (11.4)	41.5 (10.9)	37.8 (11.4)	4.68	166	0.011[c]
MOS – Mental component subscore	35.7 (10.6)	32.0 (9.2)	30.5 (8.3)	3.86	166	0.023[c]
Interpersonal Support Evaluation List total	35.4 (7.2)	32.8 (7.9)	30.7 (8.6)	4.48	169	0.013[c]
Quality of Well Being total	0.52 (0.12)	0.50 (0.13)	0.46 (0.11)	2.85	168	0.061

[1] Denominator degrees of freedom for *F* ratios, numerator df =2.

[2] Natural log transformation prior to statistical comparison.

[a] Tukey post-hoc: Full differ from partial responders.

[b] Tukey post-hoc: Full and partial responders differ from non responders.

[c] Tukey post-hoc: Full responders differ from non responders.