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Neuroticism but not omega-3 fatty acid levels correlate with early responsiveness to escitalopram

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Abstract

Background—Omega-3 fatty acid (O3FA) levels and dimensional personality measures have been associated with major depression and the course of depressive illness. We sought to study the utility of O3FA levels and dimensional personality measures as predictors of early improvement with escitalopram.

Methods—Twenty-four participants were enrolled in an open-label trial of escitalopram 10 mg/d for 4 weeks. Baseline erythrocyte O3 levels and dimensional personal assessments were obtained.

Results—Using a conservative, intention-to-treat analysis, baseline neuroticism ($r = -0.57$; $P = .007$), as measured by the Revised NEO Personality Inventory (NEO-PI-R) but not erythrocyte O3 levels, was correlated with improvements on escitalopram. A facet analysis of the neuroticism domain showed the relationship with antidepressant response to be focused on trait anxiety ($r = -0.65$; $P = .002$).

Conclusions—Anxiety may have important prognostic implications on subsequent response to selective serotonin reuptake inhibitors, such as escitalopram.

Keywords

omega-3 fatty acids; anxiety; major depression; neuroticism; antidepressant

Introduction

Although selective serotonin reuptake inhibitor (SSRI) antidepressants have been in wide use for more than 2 decades, there are no well-replicated and clinically practical predictors

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of response, other than overall chronicity and severity. In this article, we assess the potential of 2 measures—one based on erythrocyte omega-3 (O3) concentrations and the second on a self-report personality measure.

Growing evidence suggests a role of O3FA in major depression, although O3 values have not been assessed as predictors of antidepressant response. Ecologic studies demonstrated an inverse relationship between dietary O3 consumption and major depression prevalence.[1] Case-control and cross-sectional studies have further associated low serum or erythrocyte O3 levels with depression.[2–7] One large Finnish study failed to replicate these findings, although the average dietary O3 intake for the sample was quite high, at an estimated 2.2 g/d.[8] Most,[9–13] though not all,[14–17] randomized control data have shown a benefit of O3FA in major depression. A meta-analysis of 8 studies using at least 1 g/d of essential fatty acids for mood disorders favored a benefit of O3.[18] Another meta-analysis of 10 studies without dose criteria reached similar conclusions.[19] However, a funnel plot of available data suggests the possibility of publication bias, with smaller, negative studies underrepresented in the literature.[20]

There has also been limited study of the well-established 5-factor model of personality on antidepressant response. Low levels of neuroticism have been found to favor antidepressant response in some[21–24] but not all studies.[25–28] Despite the general association between neuroticism—variously defined—and poor outcome in depression,[29–31] the 3 studies using the well-validated 5-factor model in major depression did not support an association with antidepressant response.[25,27,28] It has been suggested that neuroticism decreases with treatment response[27,32,33] and may even mediate treatment response.[34] Neuroticism also appears to reduce response to prophylactic lithium in mood disorders.[35] Findings for factors beyond neuroticism have been even less consistent: Better outcomes were associated with high agreeableness in one study[27] and with extraversion in another.[28]

With growing evidence for a role of O3FA in depression, we designed a protocol to determine whether erythrocyte measures of fatty acid membrane composition predict symptom improvement during treatment of major depressive disorder (MDD) with the SSRI escitalopram. We hypothesized that patients with high O3, specifically eicosapentaenoic acid (EPA), levels would be more likely to respond to antidepressants. We secondarily sought to determine if dimensional personality variables would predict antidepressant response, and hypothesized that neuroticism would be associated with an attenuated response.

Methods

The study consisted of a 2-phase clinical trial of O3FA for prospectively defined escitalopram nonresponders. This article presents findings from phase 1—a 4-week, open-label trial of escitalopram for major depression. All study procedures were reviewed and approved by the University of Iowa Institutional Review Board.

Participants, age 18 to 55 with a current diagnosis of MDD, were recruited by advertisements, brochures, and clinician referrals. Diagnosis was confirmed by a clinician diagnostic interview and the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I). Exclusion criteria included substance abuse in the past month or dependence in the past year, an eating disorder in the past year, an allergy to fish, a bleeding disorder, plans to initiate psychotherapy during the study, pregnancy, and taking medications known to produce affective symptoms. Patients were further excluded if they were taking warfarin or had taken O3FA supplements or antidepressants for 3 or more days in the past 4 months. Those taking a stable dose of the same antidepressant agent for at least 4 weeks were

allowed entry in the study, but escitalopram was substituted. Any participant with a history of nonresponse to escitalopram or with more than 2 failed adequate antidepressant trials during the current episode was also excluded.

Participants were treated with open-label escitalopram, 10 mg/d at a fixed dose for 4 weeks. At intake, participants had a blood draw for erythrocyte O3 levels, and a dimensional assessment of personality was made with the Revised NEO Personality Inventory (NEO-PI-R),[36] with scoring upon individual completion of the study. NEO-PI-R ratings were obtained by self-report to provide a dimensional assessment of 5 major domains of personality—neuroticism, extraversion, openness, agreeableness, and conscientiousness—with additional measures of the facets or traits that define each domain.[37] One investigator (J.G.F.) performed mood ratings using the Montgomery-Åsberg Depression Rating Scale (MADRS),[38] administered weekly and by telephone in weeks 1 and 3,[39,40] as the primary outcome measure, with response defined as the total change in MADRS score.

Laboratory analysis

Fatty acid composition was determined in washed erythrocytes isolated from venous blood drawn into chilled polypropylene tubes containing EDTA (ethylenediaminetetraacetic acid) as the anticoagulant. Lipids were extracted with an isopropanol-chloroform mixture.[41,42] Following addition of butylated hydroxytoluene as an antioxidant, the lipids were dried under nitrogen, margaric acid was added as an internal standard, and the fatty acids were hydrolyzed by saponification. After the nonsaponifiable lipid was removed, the isolated fatty acids were dried, methylated,[43] taken up in carbon disulfide, and analyzed by gas-liquid chromatography.[44,45] The erythrocyte fatty acids were identified from the retention times of fatty acid methyl esters standard mixtures (Supelco Inc., Bellefonte, PA) and the weight percentage of each fatty acid calculated. The average from samples obtained at baseline and week 4 was used in subsequent analyses.

Data analysis

Data were analyzed using a modified intention-to-treat (ITT) analysis, for which all participants with available data and at least 1 follow-up assessment were included and the last observation carried forward. For our primary aim, the relationship between improvements in MADRS score and fatty acids was assessed using Pearson correlations. Fatty acids of interest included total O3, EPA, docosahexaenoic acid (DHA), total omega-6 (O6), and arachidonic acid (AA). For the secondary aims, Pearson correlations assessed the relationship between change in MADRS and each of the 5 dimensional personality domains of the NEO-PI-R at baseline, using raw scores. If a significant association was observed for a domain, correlations with change in MADRS for facets of that domain were explored. Control for multiple comparisons with primary and secondary aims used Holm's sequential Bonferroni method to maintain experimental type I error rates at a desired 2-tailed $\alpha = .05$. The assumptions of the ITT analysis were tested in a follow-up completer analysis.

Results

Of 72 participants screened, 24 ultimately qualified and provided consent for participation in the study. There was one screen failure for pregnancy. One participant did not complete any follow-up assessment, and another 4 participants dropped out before phase 1 was complete (Figure 1). One participant did not complete the NEO-PI-R at baseline, and another did not have an erythrocyte fatty acid analysis available.

Demographic and clinical characteristics of the sample are detailed in the Table. The majority of participants were female. MADRS scores at baseline ranged from 18 to 43, with

a mean score of 29, consistent with moderate depression. Of the 22 participants with at least one follow-up assessment, the mean (SD) improvement in MADRS was 11 (9). The mean (SD) MADRS at last study visit was 18 (9) and the response rate, defined as a 50% reduction in symptoms, was 27%. Based on self-report on intake history, participants did not respond to a mean of 1.0 prior antidepressant medications in their lifetime. Only 2 participants had 3 prior unsuccessful trials lifetime, and each had previously responded to one antidepressant.

Participants had a mean (SD) percent distribution of total O3FA of 6.9% (3.4%), with 0.7% (0.8%) EPA and 3.2% (1.7%) DHA, comparable to reports from large studies of adults in the United States,[46] although lower than those reported in Europe and Japan.[47–49] Total O6FA was 34.8% (4.6%), with 16.3% (2.3%) AA. Neither total O3 nor EPA levels predicted response to escitalopram. In this modified ITT sample with available data (n = 21), MADRS improvement was not correlated with total O3 ($r = -0.12$; $P = .6$), EPA ($r = -0.27$; $P = .2$), DHA ($r = -0.22$; $P = .3$), O6 ($r = -0.22$; $P = .3$), or AA ($r = 0.06$; $P = .8$).

Mean (SD) raw scores for the 5 domains of the NEO-PI-R were 124 (19) for neuroticism, 92 (18) for extraversion, 119 (28) for openness, 121 (16) for agreeableness, and 93 (17) for conscientiousness. Of those with available data in the modified ITT sample (n = 21), neuroticism was inversely correlated with improvement in MADRS over 4 weeks of treatment with escitalopram ($r = -0.57$; $P = .007$). NEO-PI-R domains of extraversion, agreeableness, openness, and conscientiousness did not appear to be related to change in MADRS. Analysis of neuroticism facets revealed a statistically significant association only for the anxiety facet ($r = -0.65$; $P = .002$), not the angry hostility, depression, self-consciousness, impulsiveness, or vulnerability facets. This relationship between the broad domain of neuroticism and the focused facet of anxiety with subsequent changes in MADRS are illustrated in Figure 2. Similar, statistically significant results were seen in a follow-up completer analysis (n = 17).

Discussion

Our results demonstrate a significantly negative relationship between neuroticism—more specifically, anxiety—with subsequent response to a 4-week course of escitalopram. Although the strong correlation may be spurious, this finding persisted on a follow-up completer analysis. There is also some, albeit inconsistent, support in the literature for this finding. Contrary to our initial hypothesis, O3FA levels did not predict early antidepressant response; in fact, a trend was observed in the opposite direction in this small sample. One could alternatively hypothesize that, given the associations between DHA depletion and low serotonin levels,[50] those with lower O3FA levels may be more likely to respond to treatment with escitalopram.

Studies of personality and antidepressant response have produced varied results and have had substantial methodological variation, including that related to the measurement of neuroticism. Only 2 studies have assessed neuroticism using the NEO-PI, a more comprehensive and contemporary assessment.[21,28] Of these studies, Bagby et al allowed treatment with any antidepressants over 5 weeks; they found extraversion but not neuroticism to predict response, although neuroticism was correlated with depression indices at the onset and conclusion of the study, and analyses of facets as predictors were not reported.[28] Tanum et al used mianserin for the treatment of functional gastrointestinal disorders, not depression, and found that those whose pain did not remit had higher baseline neuroticism raw scores. Neither study used the current revision of the NEO, the NEO-PI-R. Two studies using the abbreviated NEO Five-Factor Inventory (NEO-FFI) found no differences in neuroticism indices between responders and nonresponders.[25,27] The NEO-

FFI provides only information on personality domains and does not allow a more refined facet analysis, as performed in our follow-up analysis. Other studies have used clinician assessment or the Eysenck Personality Inventory, in which neuroticism is less reliably or more broadly defined.[23,24,26,51]

Our refined analysis demonstrated the strongest association for the anxiety facet within the domain of neuroticism. The NEO-PI-R is a self-report measure, and questions for anxiety include—though are not limited to—"I am not a worrier" (reverse scored), "I am easily frightened," and "I often feel tense and jittery." Anxiety as measured by the self-report NEO-PI-R is a personality trait, which may be amplified in the setting of major depression.[32] The apparent focus of our finding on a more narrowly defined facet within neuroticism may explain the discrepancy on prior findings. Trait anxiety or an anxious temperament has long been suggested as a predisposing factor for depression,[52,53] although it has not been studied for antidepressant response as conceptualized by the NEO-PI-R. Recent reports from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial suggest that those with a categorically defined anxious depression differ in terms of baseline characteristics and are less likely to remit on antidepressants.[54,55] Based on these findings, Fava et al concluded that anxious depression may be a valid diagnostic subtype of MDD.[55] Extending these categorical conclusions, our findings suggest that a dimensional measure of anxiety may further have predictive validity.

Recent studies have suggested an association between serotonin receptor binding and neuroticism,[56,57] and variants of the serotonin transporter gene have been associated both with neuroticism and anxiety-related traits.[58,59] The lower functioning variants of the promoter for the serotonin transporter gene, reduced to the short allele in most studies, have further been linked to reduced antidepressant response.[60] Our findings may imitate such variations in serotoninergic function or, more likely, reflect even more complex genotype or gene-environment interactions. Mechanistic considerations aside, these findings, if replicated, may be clinically useful.

There are several important limitations of this study. This sample size limits statistical power, although a statistically significant finding was identified. The magnitude of the observed effect is admittedly greater than would be expected and may be exaggerated in this small sample. Our sample included patients who had not been responding to a stable dose of an antidepressant, which may select for nonresponders in the current episode. Exclusion criteria were reported in brochures and to referring sources, so our enrollment rate following screening may overestimate the true generalizability of this finding to populations with major depression. Although our trial used recommended starting doses for escitalopram, rapid titration of serotonergic antidepressants may be associated with worsening anxiety, particularly in anxiety-prone individuals. This phenomenon has been referred to as the "jitteriness syndrome"[61] and could perhaps have attenuated clinical improvement. A relatively low dose of escitalopram was used in this study, and some clinicians may have titrated more quickly to higher doses, particularly for those patients not previously responding to a stable dose of an antidepressant. However, this approach does not improve response rates,[62] and given the elevated risk of worsening anxiety with rapid titration of antidepressants in anxiety-prone individuals, a more aggressive titration would have been unlikely to weaken the association observed. Patients on prior antidepressants were directly transitioned to escitalopram, which could result in a discontinuation syndrome, although no such symptoms were observed. Strengths of our study include our use of a rigorous erythrocyte O3FA analysis, use of a fixed-dose of a single antidepressant over a consistent time period, and use of the comprehensive and contemporary NEO-PI-R. Our use of continuous variables in the analysis further improved statistical power and mitigated the risk of our findings simply reflecting an artifact of dichotomization.

Conclusions

Although our analyses failed to support a relationship between higher O3FA levels and improvements with escitalopram, trait anxiety was revealed as a potential predictor of early improvement, with important prognostic implications regarding subsequent response to SSRIs, such as escitalopram. Psychological predictors of response have long been suspected by clinicians and could have considerable utility, although research has failed to deliver reliable psychological predictors. A larger, confirmatory study focusing on refined neuroticism facets is needed to confirm this finding, which must be considered preliminary.

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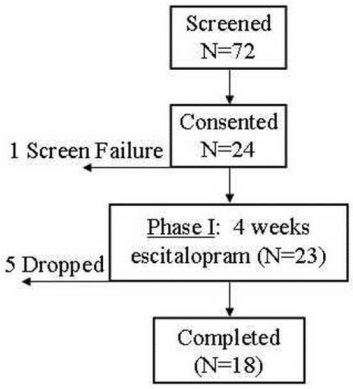

Figure 1. Flow of participants

A total of 72 potential participants were screened for eligibility, of whom 24 consented to participate in the study. There was one screen failure for pregnancy. Five participants dropped out before completion of the 4-week trial, 4 of whom had at least one follow-up assessment.

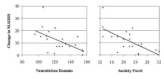

Figure 2. Relationship between neuroticism and antidepressant response

MADRS: Montgomery-Åsberg Depression Rating Scale; NEO-PI-R: Revised NEO Personality Inventory.

As evident in the scatterplot (left), the domain of neuroticism was highly correlated with change in the MADRS while on escitalopram 10 mg/d ($r = -0.57$; $P = .007$). This association was further confined to the neuroticism facet of anxiety ($r = -0.65$; $P = .002$), as illustrated in the adjacent scatterplot (right). Raw scores on the NEO-PI-R were used for domains and facets.

Table

Demographic and clinical data of participants beginning phase 1 of the study (n = 23)*

Patient characteristic	Mean (SD)
Age	31 (11)
Years of education	14 (2)
MADRS	29[a] (9)
	No. (%)
Gender	
Female	17 (74%)
Race	
African American	3 (13%)
Asian/Pacific Islander	2 (9%)
Caucasian	18 (78%)
Ethnicity	
Hispanic	2 (9%)
Marital status	
Married	11 (48%)
Separated/divorced	5 (22%)
Single	6 (26%)
Widowed	1 (4%)
Psychiatric history	
Prior psychiatric hospitalization	6 (26%)
Prior suicide attempt	5 (22%)
Prior alcohol abuse/dependence	4 (17%)
Prior drug abuse/dependence	3 (13%)

MADRS: Montgomery-Åsberg Depression Rating Scale.

*Of 24 consenting participants, there was one screen failure (for pregnancy).

[a]Consistent with moderate depression.