Selective Serotonin Reuptake Inhibitors and Endothelial Function in Women

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Abstract

Background: Among women worldwide, major depression (MDD) and heart disease rank first and second, respectively, in burden of disease. Although selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed, possible inhibition of nitric oxide (NO) function has caused concerns about their effects on protective vascular mechanisms. Our study aimed to determine the effect of SSRIs on flow-mediated vascular dilatation (FMD), platelet aggregation, and platelet NO production among women.

Methods: Women ($n=28$) without known cardiovascular disease were recruited prior to undergoing SSRI treatment for MDD, postpartum depression (PPD), or premenstrual dysphoric disorder (PMDD). Symptoms were quantified using the Hamilton Depression/Anxiety and Beck Depression scales. FMD, platelet aggregation, and platelet NO production were measured before and after 1 month of SSRI (sertraline, fluoxetine, or paroxetine) therapy.

Results: Depression and anxiety symptoms decreased significantly with SSRI treatment ($ps < 0.01$). FMD and platelet aggregation did not differ between pre- and posttreatment, although FMD rose to the normal range ($\geq 8\%$) in two of three women with abnormal FMD prior to SSRI treatment. We observed a 21% decrease ($p=0.024$) in platelet NO production.

Conclusions: SSRI treatment had little effect on FMD or platelet aggregation. The health impact of decreased NO production is unclear, particularly in this relatively young group of women without cardiovascular disease, but should be considered in future studies focusing on SSRI safety in patients with cardiovascular disease.

Introduction

COMPARED TO MEN,¹ WOMEN HAVE TWICE the lifetime risk of depression, which is associated with increased cardiovascular disease risk.² Alterations in endothelial and platelet function may underlie the association between cardiovascular disease and depression.^{3,4} Flow-mediated dilatation (FMD), the degree of brachial artery vasodilation in response to brief ischemia, provides a noninvasive measure of endothelial function.^{5,6} Individuals with major depression (MDD) showed attenuated FMD when compared with matched controls for age, gender, and risk factor.^{7,8} Among postmenopausal women, both present and past episodes of

anxiety or depression were associated with abnormal FMD, suggesting that affective disorder episodes have an enduring effect on cardiovascular health.^{9,10}

Similarly, abnormal platelet function is a common factor between cardiovascular disease and depression. Individuals with MDD, particularly women, exhibit risk for increased platelet aggregation.^{11,12} Platelet nitric oxide (NO) production, which may influence platelet aggregation,^{13–15} is dysregulated among cardiovascular patients^{16,17} and depressed individuals.¹⁸

The impact of depression on cardiovascular health may be buffered by antidepressant medications. Several but not all¹⁹ studies have shown a favorable effect of selective serotonin

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reuptake inhibitors (SSRIs) on cardiovascular health,^{20,21} including improved FMD²² and reduced platelet activation or aggregation.²³ Given the potential lasting effects of depression and anxiety on cardiovascular disease risk, we sought to examine the effects of SSRI treatment on FMD, platelet NO production, and platelet aggregation in women with affective disorders across the reproductive lifespan.

Materials and Methods

The study was a single-center, 4-week, nonrandomized, open-label study of SSRI treatment in a convenience sample of women with MDD, premenstrual dysphoric disorder (PMDD), or postpartum depression (PPD). Participants were recruited from a university-based women's mental health program, were in good physical health, and met criteria for MDD or PMDD according to the Structured Clinical Interview for Diagnostic and Statistical Manual (DSM-IV)²⁴ and prospective daily ratings (Daily Record of Severity of Problems [DRSP]²⁵) in women with PMDD. Those with MDD onset within 4 weeks of childbirth were classified as having PPD. All participants were evaluated by a third- or fourth-year psychiatry resident under the supervision of the program director (C. Neill Epperson). Participant inclusion criteria were being female and ages 18–55 years, proficient in written and spoken English, having either regular menstrual cycles of 24–39 days duration for premenopausal women or no menses for at least 12 months for postmenopausal women, and meeting criteria at screening for current MDD, PMDD, or PPD per the DSM-IV²⁶ as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I); women with PMDD underwent 2 months of prospective daily ratings using the DRSP²⁵ to confirm diagnosis of PMDD. Exclusion criteria were suicidal ideation, comorbid DSM-IV Axis I disorder, lifetime history of a psychotic disorder, documented coronary artery disease (CAD), cardiomyopathy or congestive heart failure, previous intolerance to the prescribed antidepressant medication, prior revascularization procedure in the arm, active substance use (confirmed via urine toxicology screens), pregnancy, or two or more of the following risk factors for CAD: use of more than one pack of cigarettes per week, diabetes, hypertension, hyperlipidemia, or known homocysteinemia. One of the principal investigators described the study in a face-to-face meeting for eligible, interested potential participants and described the potential risks and benefits in full. If, following this discussion, the woman remained interested in the study, written informed consent was obtained from her on the consent form approved by the Yale University Human Investigation Committee. This study predated ClinicalTrials.gov requirements and so was not registered on ClinicalTrials.gov.

Study visits

Participants attended two study visits: a baseline visit and a posttreatment visit following 4 weeks of SSRI treatment. At the baseline visit, demographic data were collected. Participants were prescribed citalopram (Celexa®) (Forest Laboratories, New York), fluoxetine (Prozac®) (Eli Lilly & Company, Indianapolis, IN), or sertraline (Zoloft®) (Pfizer Inc., New York), with starting doses of 20 mg, 20 mg, and 50 mg, respectively. The principal investigator (C. Neill Epperson) prescribed SSRI based on history of SSRI re-

sponse. Psychologic assessments, FMD measurement, and a blood draw were conducted at both visits, 4 weeks apart.

Psychologic assessments. Depression symptoms were assessed with the Hamilton Rating Scale for Depression (HAM-D)²⁷ and the Beck Depression Inventory (BDI).²⁸ Anxiety symptoms were assessed with the Hamilton Rating Scale for Anxiety (HAM-A).²⁹

Flow-mediated dilation ultrasound protocol. FMD was performed using previously described techniques.³⁰ Participants were required to fast beginning at midnight prior to the FMD ultrasound and were asked to not take any medications prior to the ultrasound, exercise during the 3 hours leading up to the ultrasound, or smoke any cigarettes for 8 hours leading up to the ultrasound. Participants arrived at the laboratory between 7 a.m. and 8 a.m. To minimize variability based on menstrual cycle, FMD was performed at same time in the menstrual cycle for menstruating women at each visit. Participants were asked to lie quietly for 10 minutes prior to the ultrasound in a quiet, temperature-controlled room. A single sonographer performed the standardized protocol. The sonographer was trained in FMD measurements and followed strict adherence to the protocol to minimize variation in data acquisition. Briefly, the right brachial artery was visualized utilizing a 12.5 MHz linear array ultrasound transducer (ATL System and Software, Philips, Andover, MA). A resting scan was obtained and arterial flow velocity was measured with a pulsed-Doppler signal at 60 degrees to the vessel in the center of the artery with the range gate of 1.5 mm. A pneumatic cuff on the upper arm was inflated to 300 mm Hg. Absence of flow through the brachial artery was confirmed by Doppler. The cuff was deflated after 5 minutes. A repeat scan of arterial flow and diameter was performed continuously for the first 15–75 seconds after deflation, followed by a 10-minute resting period. To define an endothelial independent measurement of brachial artery dilatation, a baseline scan was repeated and 0.4 mg sublingual nitroglycerin administered, followed by a repeat scan of brachial artery diameter. FMD was calculated as the change in posthyperemia diameter as a percentage of the baseline diameter.³¹

Blood draw. Blood was collected for platelet aggregation, NO production, and hormone assays. Standard phlebotomy techniques were used to draw 15 mL of whole blood. To minimize variability based on menstrual cycle, phlebotomy was performed at the same time in the menstrual cycle for menstruating women at each visit.

Platelet aggregation. Whole blood was collected and platelets were prepared according to standard methods.^{32,33} The column was packed and washed with a buffered solution. The buffer was adjusted to the correct pH, and the platelet count was normalized to 100,000 platelets per mL with a modified solution. Five μ M adenosine diphosphate (ADP) was used to stimulate aggregation, which was recorded using a Chronolog aggregometer (Chrono-Log, Havertown, PA).³⁴ Results were digitized and converted to a KaleidaGraph file for analysis.

NO production. A specialized NO-specific probe—inNO-T Nitric Oxide Measurement System (Harvard

Apparatus, Holliston, MA)—was placed in the cuvette, using a customized plexiglass holder. The probe was calibrated using two standard concentrations of NONOate. Gel-filtered platelets were placed in the aggregometer cuvette in a concentration of 100,000 platelets per mL. Platelet aggregation was stimulated utilizing 5 μ M ADP. NO concentrations were continuously recorded during aggregation.

Estrogen, progesterone assays. Serum estradiol and progesterone levels were determined in a commercial laboratory, using heterogeneous competitive magnetic separation assay with a lower limit of detection (LOD) of 30.7 pmol/L and immunoassay techniques with a within-run coefficient of variation (CV) of 8.1% at the LOD for estradiol and a LOD of 0.32 nmol/L and CV of 9.3% for progesterone.

Statistical analysis

The study was powered to detect a 5% change in the primary outcome variable, FMD, between treatment groups with 90% confidence. Histograms and 5% trimmed mean parameters were used to assess outliers. Bivariate correlation and analysis of variance (ANOVA) were used to examine group differences. Pre- and posttreatment results in outcome measures were compared using repeated-measure ANOVA. Data analyses were carried out using SPSS software, version 20 (SPSS Inc., Chicago, IL).

Results

Twenty-seven of the 28 women who were enrolled completed all aspects of the study. Participant characteristics are depicted in Table 1. Among medication treatment groups, there were no statistically significant differences in age ($F [2,24]=0.194$, $p=0.825$), race ($\chi^2(4)=2.76$, $p=0.600$), reproductive status ($\chi^2(4)=1.57$, $p=0.813$), or diagnosis ($\chi^2(4)=3.15$, $p=0.534$). Thus, these variables were not considered covariates in the following analyses. One participant smoked cigarettes (<1 pack per day); no other participants

had aforementioned cardiovascular risk factors. Among women in the postpartum group ($n=5$), months postpartum was mean (M)=2.10 (standard deviation [SD]=1.7). Eight women were assigned to citalopram, 7 to fluoxetine, and 12 to sertraline. Maximum doses were 40 mg citalopram (M 21.43 mg), 20 mg fluoxetine (M 20 mg), and 125 mg sertraline (M 72.5 mg). In addition to the study SSRI, some participants were taking lorazepam ($n=3$), hormonal contraceptives ($n=3$), estradiol patch ($n=2$), or risperidone ($n=1$). Of the 27 participants, none discontinued medication. Side effects were consistent with those commonly reported with these agents.³⁵ No adverse events were reported, and no participants dropped owing to side effects or adverse events.

Flow-mediated dilatation

Overall, FMD decreased by 1.2 percentage points with SSRI treatment (18.8% pretreatment, 17.6% posttreatment); however, this was nonsignificant ($F(1,24)=2.38$, $p=0.14$) (Table 2). Among subjects receiving citalopram, FMD decreased by 4.1%. Among subjects receiving fluoxetine, FMD decreased by 3.4%. Among subjects receiving sertraline, FMD increased by 1.9%. Brachial artery diameter averaged $M=3.0$ mm pretreatment (citalopram 3.0 mm, fluoxetine 3.1 mm, sertraline 2.9 mm) and remained at $M=3.0$ mm posttreatment (citalopram 3.2 mm, fluoxetine 3.1 mm, sertraline 2.9 mm). There were no significant group differences by age, race, reproductive status, diagnosis, or treatment group in FMD at pre- or posttreatment and no significant correlations between change in FMD over treatment and any of these demographic characteristics. Changes in FMD were not significantly correlated with changes in BDI ($r=-0.006$, $p=0.98$), HAM-D ($r=0.226$, $p=0.27$), or HAM-A scores ($r=0.210$, $p=0.31$). Finally, there were no significant differences in the initial resting scan at pre- versus posttreatment, indicating good interscan reliability ($t(26)=-1.16$, $p=0.26$).

Platelet aggregation

There was a mean increase in platelet aggregation by 2.21% in this sample, which was nonsignificant ($F[1,24]=0.35$,

TABLE 1. PARTICIPANT DEMOGRAPHIC AND DIAGNOSIS CHARACTERISTICS

Variable	Citalopram (n=8)	Fluoxetine (n=7)	Sertraline (n=12)	Total (n=27)
Age M (SD)	37.3 (9.7)	37 (5.3)	39.1 (8.3)	38 (7.9)
Race (n)				
African American	2	0	1	3
Caucasian	5	6	10	21
Hispanic	1	1	1	3
Reproductive status (n)				
Menstruating	6	5	6	17
Postpartum, no menses	1	1	3	5
Menopausal	1	1	3	5
Diagnosis (n)				
MDD	3	4	7	14
PMDD	1	2	1	4
PPD	4	1	4	9

M, mean; MDD, major depressive disorder; PMDD, premenstrual dysphoric disorder; PPD, postpartum depression; SD, standard deviation.

TABLE 2. PSYCHOLOGIC AND CARDIOVASCULAR OUTCOMES

Variable: M (SD)	Pretreatment	Posttreatment	p
BDI	22.8 (9.5)	11.6 (6.7)	<0.01 ^a
HAM-D	18.0 (5.9)	10.3 (7.0)	<0.01 ^a
HAM-A	17.2 (6.3)	9.4 (5.2)	<0.01 ^a
Brachial Artery Diameter (mm)	3.0 (0.4)	3.0 (0.3)	0.26
FMD (% change)	18.8 (7.7)	17.6 (7.7)	0.14
FMD-N (% change)	23.7 (9.4)	24.3 (8.9)	0.32
Platelet aggregation (% change)	26.7 (3.8)	27.3 (3.8)	0.56
Platelet NO, pmol/10 ⁸ platelets	9.8 (4.6)	7.7 (3.2)	0.02 ^a

FMD calculated as ([Posthyperemia] – [Prehyperemia]) / [Prehyperemia] $\times 100$.

^a $p < 0.05$.

BDI, Beck Depression Inventory; FMD, flow-mediated dilatation; FMD-N, FMD nitroglycerin-induced; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; NO, nitric oxide.

$p=0.56$) (Table 2). Among subjects receiving citalopram, platelet aggregation increased by 2.8%. Among subjects receiving fluoxetine, platelet aggregation increased by 4.8%. Among subjects receiving sertraline, platelet aggregation increased by 0.3%. There were no significant group differences by age, race, reproductive status, diagnosis, or treatment group in platelet aggregation at pre- or posttreatment and no differences observed in platelet aggregation between treatment groups ($F[2, 24]=0.217, p=0.81$).

Platelet NO production

There was a significant 21% decrease in platelet NO production with SSRI treatment ($F[1,24]=5.775, p=0.02$) (Table 2). Among subjects receiving citalopram, NO production decreased by 13.3%. Among subjects receiving fluoxetine, NO production decreased by 33%. Among subjects receiving sertraline, NO production decreased by 18.9%. There were no significant group differences by age, race, reproductive status, diagnosis, or treatment group in platelet NO production at pre- or posttreatment and no differences in platelet NO production between treatment groups posttreatment ($F[2, 24]=0.665, p=0.52$).

Estrogen, progesterone

There was a significant correlation between progesterone level and age ($r=-0.42, p=0.03$), but hormone levels were not significantly correlated with any psychologic or cardiovascular outcome variables, except estrogen, which was inversely correlated with platelet NO production at pretreatment ($r=-0.4, p=0.02$). There were no significant group differences by age, race, diagnosis, or reproductive status in estrogen or progesterone measures at pre- or posttreatment. There were no significant differences in cardiovascular outcome variables between hormone users ($n=5$) and nonusers.

Psychologic outcomes

Overall, BDI scores decreased by 48.9%, HAM-D scores decreased by 42.6%, and HAM-A scores decreased by 45.4% ($ps<0.01$) (Table 2). There were no significant group differences by age, race, or treatment group in psychologic outcome measures at pre- or posttreatment. As PMDD is distinct from MDD, we examined group differences among diagnoses. At pretreatment, MDD and PPD participants showed significantly higher BDI ($F[2,24]=5.67, p=0.001$) and HAM-D ($F[2,23]=5.02, p=0.02$) scores than PMDD participants, but at posttreatment, mean scores had equalized among groups. All three antidepressant agents were effective in relieving depressive and anxious symptoms.

Discussion

This study was unique in assessing cardiovascular risk markers in women with common affective disturbances across the reproductive lifespan.^{7,8,36} Previous studies examined FMD in women with premenstrual syndrome (PMS)³⁷ or healthy women in the postpartum³⁸ but did not assess the impact of SSRI treatment.

Although participants experienced significant improvement in mood, changes in cardiovascular markers with SSRI treatment were largely unremarkable. Previous research has

shown impaired FMD in participants with MDD, with mean scores falling below 10%^{7,10,19,22} and improvement in FMD with sertraline treatment.²² However, in this sample, FMD means were 18.8% and 17.6% at pre- and posttreatment, respectively. Thus, it is possible that significant improvements in FMD with SSRI treatment were not seen, owing to a ceiling effect; FMD was not impaired at baseline, so there was little room for improvement. Indeed, of the three participants who fell in the clinically “abnormal” range (FMD < 8%)³⁹ pretreatment, two reverted to the normal range with SSRI treatment. Using a more conservative FMD < 5%³⁹ as abnormal, one participant fell in the “abnormal” range pretreatment and reverted to the normal range with SSRI treatment. Several previous studies demonstrating FMD improvement with SSRI treatment allowed concomitant use of cardiovascular medications.^{9,10,19,22} The present participants were healthy in terms of cardiovascular function, such that they were not taking concomitant cardiovascular medications but were also less likely to have abnormal FMD at baseline. It is possible that 4 weeks was an insufficient treatment period; previous research showing FMD improvement with SSRI treatment used a treatment period of 20 weeks.²²

Unlike previous research,^{40–42} we did not observe an impact of SSRI treatment on platelet aggregation. However, our results indicated that another marker of platelet function, platelet NO production, decreased considerably with SSRI treatment, with a significant 21% drop from pre- to posttreatment. Interestingly, platelet NO production decreased while platelet aggregation did not change; this is consistent with research showing that platelet NO production does not necessarily modulate platelet aggregation,^{13,43} despite early studies suggesting a relationship. Or, platelet NO production may precede clinical changes in vascular function, such as FMD⁴⁴; longer SSRI treatment duration may have shown more significant vascular effects. The literature regarding SSRI effects on platelet NO production is highly mixed, with some studies showing SSRI treatment leading to decreased (citalopram⁴⁵), no effect (paroxetine⁴⁶), or increased (paroxetine^{18,47}) plasma NO levels with no effect on nitric oxide synthase (NOS) activity observed in some studies.¹⁸ The connection between NO function and depression is complex, particularly in that plasma levels of NO do not specifically reflect platelet or endothelial NO production. For instance, the present study did not assess NOS function, which may also influence this relationship. Although SSRI inhibition of NOS function has been described in multiple settings, the effect may vary among populations,⁴⁸ mode of administration,⁴⁹ and within the class of agents.⁵⁰

The present study had a number of strengths, including strict diagnostic procedures, exclusion of concomitant medications that could affect outcomes of interest, and inclusion of women from early to mid- and late adulthood with accompanying hormonal measures. However, limitations included small sample size, lack of randomization, and lack of long-term morbidity or mortality data. Indeed, the small sample size across groups, potential heterogeneity in treatment effects, lack of randomization, and short duration of follow-up indicates that these findings be interpreted with caution. Although the small sample size precluded testing differences between SSRIs, owing to insufficient power, data

do not suggest differences among SSRIs in terms of cardiovascular outcomes.^{20,21} Still, the results should be regarded as pilot work, given limitations in analyzing secondary outcomes owing to small sample size. This was a healthy female sample, which limits generalizability of the results but enabled us to focus on the effects of SSRI without cardiovascular medications. In sum, the results of this study indicate that the SSRIs used to treat depressive and anxious symptoms in women with MDD, PMDD, and PPD had little effect on cardiovascular parameters measured during a 4-week time frame.

Conclusions

Although SSRI treatment resulted in significant improvements in depressive symptoms and anxiety among women with MDD, PMDD, and PPD, SSRIs had little effect on cardiovascular measures in this sample of young women without cardiovascular disease.

Acknowledgments

C. Neill Epperson, Josiah Child, and Christopher Howes designed the study and wrote the protocol. Kathryn A. Czarkowski coordinated the study, supervised data collection and database management, and was responsible for all institutional review board (IRB) submissions, modifications, and renewals. Liisa Hantsoo managed the literature searches, performed the statistical analysis, and wrote the first draft of the article. All authors contributed to and approved the final article.

Author Disclosure Statement

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