Depression Treatment Selectively Modifies Arterial Stiffness in Older Participants

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Background. Depression is emerging as an independent cardiovascular disease risk factor. We investigated whether treating depression in older participants impacted on arterial stiffness, a known cardiovascular disease risk factor and a clinical marker of arterial aging.

Methods. Seventy-five participants with pulse wave velocity (PWV), the gold standard measure for arterial stiffness, at baseline and at 12-month follow-up were included. Depressed patients were randomized to escitalopram (10 mg/d) or to duloxetine (60 mg/d). In patients without depression, no antidepressant therapy was started. The psychologist and the doctor measuring PWV were both unaware of antidepressant treatment.

Results. At study entry, no difference in PWV were observable in the three groups of participants. A significant time × drug interaction term (p < .05) was observed for the impact of antidepressant therapy on PWV by analysis of covariance analysis. After 12 months of therapy, duloxetine treatment resulted in a significant (+21%) and escitalopram treatment in a not significant (6%) PWV increase. These changes in PWV were accompanied by a similar increase in blood pressure and LDL cholesterol in the two treated groups. However, duloxetine resulted in a significant 10% greater heart rate after 12 months that was not observable in participants treated with escitalopram nor in not-depressed older participants. Multiple regression models revealed that a drug-specific effect on PWV persisted after controlling for cardiovascular risk factor levels.

Conclusion. Duloxetine but not escitalopram significantly increased PWV in older depressed participants after 12 months of treatment. The effect was not fully explained by concomitant changes in traditional cardiovascular risk factors known to significantly impact arterial stiffness.

Key Words: Pulse wave velocity—Arterial stiffness—Depression—Duloxetine—Escitalopram.

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ARTERIAL aging is characterized by a progressive stiffening, thickening, and enlargement of large arteries (1). Carotid-femoral pulse wave velocity (PWV), the gold standard for noninvasive measurement of arterial stiffness in clinical setting (2), is highly predictive of traditional “hard cardiovascular” end-points (stroke and myocardial infarction) (3,4), cognitive dysfunction, and dementia (5–7).

Unipolar depressive disorders are very common conditions in older participants, affecting 1%–2% of the population aged more than 65 (8), 14% of community-dwelling, and 32% of residential care-dwelling participants (9). Depressive symptoms have been associated to a greater total and cardiovascular morbidity and mortality (10–12), as well as to increased risk of hospitalization for adverse drug reaction in older participants (10–14). Dysregulation of the autonomic nervous system (15) with a reduction in the threshold for arrhythmias (15) and/or promoting procoagulant processes via platelet activation (16) have been proposed as pathophysiological factors for such an association. Recently, a reduced nocturnal fall in blood pressure and a greater 24-hour blood pressure variability have been reported in older participants with depressive symptoms (17).

Yet, to date there are no compelling evidences about mechanisms underlying the association between depression and cardiovascular (CV) events. Additionally, no study explored whether treating depression in older participants was associated with reduction in CV risk profile.

The aim of the present study was to explore whether different treatments of depression could impact arterial stiffness, a known risk factor for CV events and a clinical marker of arterial aging.
Methods

Patients
Patients were enrolled between January 2008 and July 2009. The protocols were approved by the institutional review boards, and written informed consent was obtained from each participant. A total of 200 patients were enrolled. Only participants with PWV measured at baseline and at 12 months follow-up were included in the present analysis. Inclusion criteria included age older than 70 years with newly diagnosed depression. Patients were excluded if they had acute CV events (myocardial infarction and stroke; had undergone angioplasty or cardiac/vascular surgery) in the previous year; moderate-to-severe cardiac, respiratory, or hepatic failure; renal failure (serum creatinine >2 mg/dL); disabling musculoskeletal disorder; cancer; neurodegenerative disorders such as idiopathic Parkinson disease or dementia; and had undergone treatment with antidepressant drugs. Of the 200 enrolled participants, 13 presented missing data at baseline, 75 were lost to follow-up, and 37 presented incomplete data at follow-up visits. Thus, the study population of the present study consisted of 75 older participants.

A complete physical and neurological examination was performed at the time of study entry. Body weight and height, a 12-lead electrocardiogram, as well as laboratory measures of fasting blood glucose; total and HDL cholesterol; triglycerides; blood cell count; serum sodium, potassium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total protein, and creatinine; blood urea nitrogen; uric acid; and urinalysis were obtained at the beginning of the study and 12-month follow-up.

Arterial Stiffness Measurement
Arterial stiffness was assessed noninvasively by the Carotid-femoral PWV. PWV was measured by an automate device (Complior, Artech-Medical, France), whose validation and reproducibility have been previously published (18,19). Pulse transit time was determined as the average of 10 consecutive beats. The distance travelled by the pulse wave was measured over the body surface as the distance between the two recording sites (carotid and femoral pulse). PWV was calculated as the ratio of distance to transit time. The reproducibility of PWV in our laboratory was evaluated by performing repeated measurements in 20 participants (6 men and 14 women), with an average age of 67 ± 13 years (range 40–88). The correlation between repeated measurements was 0.92. The mean difference between the two measurements was 0.08 m/s (p = .73).

Assessment of Depression
At baseline and at each follow-up interview, the patient was examined for depression. The diagnosis of depression was based on the patient meeting diagnostic criteria for major or minor depression (ie, symptom duration for 2 or more weeks) and having a Hamilton-17 Depression Rating Scale score of greater than 12.

Experimental Design and Treatment
Patients with depression were randomized to escitalopram (10 mg/d) or to duloxetine (60 mg/d). In patients without depression, no antidepressant therapy was started.

The psychologist and the doctor measuring arterial stiffness, for example, PWV, were both unaware of each patient’s antidepressant treatment assignment.

At each visit (or sooner if a participant reported an adverse event), patients and their family members were asked about adverse events.

Statistical Analysis
Means and standard deviations were calculated for continuous measures and analyses were conducted using one-way analysis of variance. Analysis of covariance analyses were conducted using PWV as the dependent variable. In addition to treatment group, follow-up time and an interaction term treatment × time, the initial models contained factors known to impact PWV as independent variables: age, sex, education, traditional CV risk factor levels, heart rate, use of antihypertensive medication, diuretic, and nitrates. Backward elimination of statistically nonsignificant terms yielded the final model, with age and sex forced into all models. PWV an traditional CV risk factor levels were introduced into the models either as absolute values or as percentage changes from baseline—calculated as 100 × (value at 12 months − value at baseline)/value at baseline).

To better understand factors underlying the different impact of antidepressant therapy on PWV, we analyzed whether the changes in CV risk factors for a period of 12 months differed among the three groups and whether the correlation between CV risk factors and PWV changes for a period of 12 months differed in the three groups of older participants.

All analyses were performed using SAS version 9.1.3 for Windows (SAS Institute Inc, Cary, North Carolina). All the p values reported are two tailed. Significance level was set at p < .05.

Results
At study entry, no difference in PWV or PWV/mean blood pressure was observable in depressed older participants treated with escitalopram or with duloxetine compared with control participants of the same age. Depressed participants, regardless of treatment, were more likely to be women. Depressed older participants treated with escitalopram had greater adiposity (BMI) and received more often antihypertensive medications, diuretics, and nitrates than depressed older participants treated with duloxetine or control participants (Table 1).
A significant interaction term between time and drug \((p < .05)\) was observed for the impact of antidepressant therapy on PWV in older participants by analysis of covariance analysis. The positive interaction term suggested that the change in PWV over time differed by treatment. Table 2 illustrates the significant factors impacting PWV in the study population.

To better visualize the implication of the significant interaction between time and antidepressant therapy, average levels of PWV were calculated at baseline and 12 months for each group—after controlling for age, sex, BMI, fasting glucose levels, systolic blood pressure (SBP), and use of antihypertensive medications. As illustrated in Figure 1, depression treatment with duloxetine resulted in a significant increase of PWV (top left panel) or PWV normalized for mean blood pressure (bottom left panel) at 12 months compared with depressed older participants treated with escitalopram or not-depressed participants.

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As illustrated in Figures 2 and 3, in the not-depressed older participant, a 6% decrease after 12 months was accompanied by an average 2.2% decrease in SBP, a 4% decrease in pulse pressure (PP) and heart rate, and an 8% decrease in LDL cholesterol levels. In the depressed older participants treated with escitalopram, a 6% increase in PWV at 12 months was accompanied by a 6% increase in SBP and PP, a virtually unchanged heart rate, and an 8% increase in the LDL cholesterol levels. When normalized for blood pressure levels, PWV was virtually unchanged after 12 months of treatment with escitalopram. Conversely, after 12 months of treatment with duloxetine, depressed older participants presented a 21% increase in PWV levels (a 18% increase when PWV was normalized for mean blood pressure) that was accompanied by a 3% increase in SBP, a 6% increase in PP, an 8.3% increase in heart rate, and a 10% increase in LDL levels.

Multiple regression analysis model revealed that treatment assignment remained a significant determinant of PWV changes for a period of 12 months \((f = 3.2; p < .05)\), independently of age, sex, and changes in SBP or in heart rate from baseline to 12 months.
Figure 1. Effect of duloxetine and escitalopram on arterial stiffness (pulse wave velocity [PWV] and PWV normalized for mean blood pressure) compared with not-depressed older participants during 12 months of treatment.

Figure 2. Effect of duloxetine and escitalopram on blood pressure and heart rate compared with control participants during 12 months of treatment.
Discussion

This is the first study investigating the impact of antidepressant therapy on arterial aging, measured as aorta PWV, in older participants. We observed that duloxetine significantly increased PWV in older depressed participants after 12 months of treatment, whereas PWV change over time in older participants treated with escitalopram was similar to what observed in older not-depressed participants. These effects on arterial stiffness were independent of blood pressure changes, or other traditional CV risk factor levels known to significantly impact arterial stiffness (1). A significant increase in heart rate accompanied duloxetine treatment.

Arterial aging is risky for CV events (1) and depression itself is emerging as an independent risk factor for CV events (20,21). Nonetheless, in spite of the high prevalence of depression in older participants at high CV risk, there is no routine screening for depression in older patients (20). Additionally, experts had suggested treatment for a first episode of depression in older participants for 6 months (22). Consistently, most available studies demonstrating the effectiveness of continued treatment of depression in elderly patients have short duration (16–24 weeks) (23–26). If the impact of depression on disability is independent of the number and the severity of comorbidities in older participants (27), yet the number and severity of concomitant medical illnesses (especially hypertension, coronary artery disease, diabetes, osteoarthritis, and chronic lung disease) may trigger mood disorder and their relapse in older participants (28–30). Thus, long-term antidepressant therapy may be appropriate in older participants (25,26). In these regards, a strength of our study is represented by the length of treatment (12 months) of depressed older participants and the evaluation of traditional and novel (arterial stiffness) risk factors for CV events. We cannot rule out that the impact of duloxetine treatment on heart rate may reflect a stronger pharmacological antidepressive effect of duloxetine because the drug impacts monoamines and cathecolamines metabolism. The differential influence of antidepressant treatments on the arterial stiffness was partly attributable to the impact of medications on traditional CV risk factor levels. However, both duloxetine and escitalopram were accompanied by a similar increase in blood pressure and in LDL cholesterol levels (a consequence of increased appetite and food intake with mood improvement in older participants) compared with not-depressed older participants. Duloxetine was also accompanied by a significant heart rate increase compared with escitalopram and not-depressed participants. However, the multiple linear regression models indicated that the differential effect of the antidepressant medication on

Figure 3. Effect of duloxetine and escitalopram on metabolic risk factors for cardiovascular disease compared with control participants during 12 months of treatment. BMI (top left panel), fasting glucose (top right panel), and HDL and LDL cholesterol (bottom panels).
arterial stiffness was not exclusively related to changes in traditional CV risk factor levels. It is beyond the scope of the present study to try to answer such a question. A recent study suggested an antidepressant drug specific effect on selected potassium channels in the cell membrane (31).

Our study design does not allow to elucidate possible mechanisms for the observed increase in PWV in older depressed participants receiving duloxetine. However, the reported increase in heart rate may play a role. In fact, arterial stiffness is largely influenced by arterial content in elastin. Increased heart rate implies a greater number of pulsation in the aorta, resulting in a greater material fatigue of the elastin (one of the most inert nonliving material in the body, with half-life of decades) and thus in an increase in aorta stiffness—as measured by PWV (32).

**Clinical Implications**

If our results will be confirmed in larger studies, the treatment of depression should also account for its impact on participants’ CV risk profile. Arterial stiffness, a surrogate of arterial aging clinically measurable noninvasively as PWV, may represent a simple and significant index of CV risk to be assessed even in older participants.

Additionally, the results of the present study provide evidence that arterial aging is not an immutable, but rather a modifiable risk factor for vascular events (33).

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**Conflict of Interest**

None declared.

**References**


