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Longitudinal Evidence for Unfavorable Effects of Antidepressants on Heart Rate Variability

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Background: It was previously shown that antidepressants are associated with diminished vagal control over the heart. Longitudinal studies are needed to test the causality of this association further.

Methods: Longitudinal data were obtained in the Netherlands Study of Depression and Anxiety. At baseline and at 2-year follow-up, heart rate and cardiac vagal control as indexed by respiratory sinus arrhythmia were measured in 2114 subjects (mean age = 42.0 years; 66.2% female), who either used antidepressants at one or two time points ($n = 603$) or did not use antidepressants at any time point ($n = 1511$). Linear mixed-model analyses were conducted to compare changes in respiratory sinus arrhythmia and heart rate over time across antidepressant-naive subjects, subjects who started using an antidepressant during follow-up, subjects who stopped using an antidepressant, and persistent antidepressant users. Analyses were adjusted for demographics, health, and lifestyle factors.

Results: Compared with continuous nonusers, subjects who started the use of a tricyclic antidepressant or a serotonergic and noradrenergic antidepressant showed a significantly greater increase in heart rate and a decrease of respiratory sinus arrhythmia at 2 years. Subjects who started the use of selective serotonin reuptake inhibitors also showed a decrease in respiratory sinus arrhythmia, but their heart rate did not increase. Discontinuing antidepressants systematically caused opposite effects; levels returned in the direction of those observed among nonusers.

Conclusions: These 2-year longitudinal results indicate that all antidepressants cause a decrease in cardiac vagal control. After discontinuing antidepressants, autonomic function recovers, suggesting that the unfavorable effects are (partly) reversible.

Key Words: Antidepressants, anxiety, cardiac vagal control, depression, heart rate, heart rate variability, respiratory sinus arrhythmia, selective serotonin reuptake inhibitors (SSRI), serotonergic and noradrenergic antidepressant (SNRI), tricyclic antidepressants (TCA)

Recent research has indicated a potential important role of antidepressant use in the dysregulation of the autonomic nervous system (ANS) that has been observed among depressed or anxious subjects (1–8; and Licht CMM, Penninx BWJH, de Geus JCN: *Cardiac sympathetic activity in major depressive and anxiety disorder: An important role for antidepressants;* unpublished data; 2010.). In these subjects, the use of tricyclic antidepressants (TCAs), serotonergic and noradrenergic antidepressants (SNRIs), and selective serotonin reuptake inhibitors (SSRIs) was associated with increased heart rate (HR) and decreased heart rate variability (HRV), whereas associations were small or even nonsignificant when HR and HRV were compared between antidepressant-naive depressed or anxious subjects and healthy control subjects (1,5,9). These results imply that depression and anxiety disorders in themselves did not cause diminished parasympathetic nervous system and increased sympathetic nervous system activity but that this effect might be driven by the effects of antidepressants. Nevertheless, previous studies were cross-sectional, which limits causal interference. It remains unclear whether the reported dysregulation of both autonomic branches in antidepressant users results completely from the effects of these drugs or whether underlying differences between patients taking and not taking antidepressants may have played a role. Longitudinal analyses, which compare within-subject changes in autonomic nervous system indicators as a function of changes in antidepressant use, can provide more definitive evidence for a causal effect of antidepressants.

This 2-year longitudinal study examined the extent to which changes in antidepressant use are associated with parallel changes in HR and HRV. It also examined whether discontinuation of antidepressants results in recovery of autonomic measures to levels seen among nonusers. The large sample size enabled us to consider important covariates and address various antidepressants classes (TCAs, SNRIs, and SSRIs).

Methods and Materials

Subjects

Subjects participating in this study came from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study conducted in 2981 subjects (18–65 years, 95.2% of northern European ancestry) to examine the long-term course of depression and anxiety disorders. The rationale, methods, and recruitment strategy have been described elsewhere (10). The NESDA sample consists of persons without depression and anxiety disorders and persons with a (remitted or current) diagnosis of depressive or anxiety disorder. To represent various settings and stages of psychopathology, depressed or anxious subjects were recruited at three locations in the Netherlands in various settings: from the general community, through a screening procedure in primary care, and through mental health care organizations. The baseline assessment lasted 4 hours on average and included assessment of demographic and health and lifestyle characteristics, a standardized diagnostic psychiatric interview, and a medical assessment. The research protocol was approved by the ethical committees of

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the participating universities, and all respondents provided written informed consent.

Two years after baseline assessment, a face-to-face follow-up assessment was conducted with a response of 87.1% (2596 of the 2981 respondents participated). Nonresponders were younger, more often of non-northern European ancestry, less educated, and more often had major depressive disorder (MDD) (Lamers F, Hoogendoorn A, Smit JH, van Dyck R, Zitman FG, Nolen WA, Penninx BWJH: *Socio-demographic and psychiatric determinants of attrition in the Netherlands study of depression and anxiety (NESDA);* unpublished data; 2010).

Patterns of Change in Antidepressant Use

First, patterns of change in MDD and anxiety disorder status were defined to rule out possible underlying effects of MDD or anxiety disorders on autonomic measures. The presence of MDD and anxiety disorders (social phobia, panic disorder with or without agoraphobia, and generalized anxiety disorder) was ascertained at both baseline and at 2-year follow-up, using the Composite International Diagnostic Interview (World Health Organization, version 2.1), which establishes diagnoses according to DSM-IV criteria (11) and has shown high interrater and test–retest reliability, as well as high validity for depressive and anxiety disorder (12). To investigate the effects of incidence or remission of MDD or anxiety disorders, persistence, remission, or recurrence of MDD and anxiety disorders were determined categorizing persons into five disorder groups: 1) persistent controls—no (lifetime) diagnoses at baseline and none at follow-up, 2) persistent remitted subjects—remitted (greater than 6 months earlier) MDD and/or anxiety diagnoses at baseline and no new onset at follow-up, 3) remission of a disorder—subjects with a current (6-month recency) diagnosis at baseline and remission at follow-up, 4) new onset of an MDD or an anxiety disorder—no diagnosis or remitted diagnosis at baseline and current diagnosis at follow-up, and 5) persons with a persistent MDD/anxiety disorder— 6 month recency of diagnosis of MDD and/or anxiety disorder at baseline as well as at follow-up.

Second, the use of various antidepressants at baseline and at follow-up was determined on the basis of drug container inspection for all drugs used in the month before assessment and was classified according to the Anatomical Therapeutic Chemical Classification (13). Use of antidepressants was considered present when taken for at least 1 month, 50% of the time, and included TCAs (Anatomical Therapeutic Chemical [ATC] code N06AA), SNRIs (ATC code N06AF/N06AX), and SSRIs (ATC code N06AB).

Patterns of change in antidepressant use were determined by categorizing subjects based on their 2-year antidepressant status as 1) persistent nonusers, consisting of persons who did not use any antidepressant at baseline and follow-up; 2) persistent users, defined as use of a specific antidepressant at both baseline and follow-up; 3) new users of an antidepressant, which was defined as no use at baseline, but use of an antidepressant at follow-up; 4) subjects who stopped using antidepressants, defined as using an antidepressant at baseline and no use at follow-up; and 5) subjects who changed from using one type of antidepressant at baseline to another type at follow-up (SSRI → SNRI, SNRI → SSRI, etc.). Thirty-two subjects were excluded because they were on multiple antidepressants at baseline or follow-up or were part of groups with less than 10 subjects (e.g., those who switched from TCAs to SSRIs). Another 22 subjects were excluded because they had other psychiatric diagnosis (e.g., dysthymia or minor depression) without an MDD or anxiety diagnosis. In addition, 428 subjects had missing physiologic data at baseline or follow-up. Consequently, data from 2114 subjects were categorized into 12 antidepressant groups: persistent nonusers ($n = 1511$), persistent TCA users ($n = 35$), persistent SNRI users ($n = 65$), persistent SSRI users ($n = 195$), new users of a TCA ($n = 12$), new users of an SNRI ($n = 23$), new users of an SSRI ($n = 74$), TCA users who stopped ($n = 10$), SNRI users who stopped ($n = 32$), SSRI users who stopped ($n = 123$), SNRI users who switched to an SSRI ($n = 10$), and SSRI users who switched to an SNRI ($n = 24$).

Physiologic Measurement

Basal respiratory sinus arrhythmia (RSA), an index of cardiac vagal control, and heart rate, an index of combined parasympathetic and sympathetic nervous system activity, were measured using the VU University (Vrije Universiteit) ambulatory monitoring system (VU-AMS). The VU-AMS is a light-weight ambulatory device that records an electrocardiogram and changes in thorax impedance (dZ) from six electrodes placed at chest and back of the subjects (14,15). An automatic scoring algorithm detected the beginning and end of inspiration and expiration in the respiration signal obtained from the filtered (.1–.4 Hz) dZ signal. Respiratory sinus arrhythmia was assessed by peak–valley estimation (pvRSA) using the combined electrocardiogram and respiration signals. Per-breath estimates of pvRSA were obtained by subtracting the shortest interbeat interval during HR acceleration in the inspirational phase from the longest interbeat interval during deceleration in the expirational phase. Automatic scoring and cleaning of respiration rate and pvRSA was checked as described earlier (1,5).

Recording is unobtrusive, and subjects maintain full freedom of movement, tending to habituate rapidly to this type of recording. NESDA subjects were wearing the VU-AMS device during assessment of the clinic visits at baseline and at 2-year follow-up. Movement registration through vertical accelerometry was used to excise periods when subjects were nonstationary. Removal of breaks and nonstationary parts (~15 min) resulted in four conditions: a supine rest condition with blood pressure measurement (baseline: 9.8 ± 3.0 min, follow-up: 9.4 ± 3.0 min) and three conditions with mild cognitive load in which the subjects were sitting upright: interview Session 1 (baseline: 37.8 ± 12.3 min, follow-up: 46.0 ± 25.9 min), interview Session 2 (baseline: 35.8 ± 12.8 min, follow-up: 32.5 ± 12.0 min), and a computer task (Implicit Association Task baseline: 16.0 ± 3.8 min, follow-up: 15.2 ± 3.4 min). The Implicit Association Task is a computerized reaction time task designed to measure implicit associations between self-describing items and anxiety- and depression-related items (16), rather than to induce autonomic response. Exploratory mixed-model analyses revealed that differences between antidepressants groups (and patterns of MDD/anxiety groups) were comparable in the various interview conditions at baseline as well as follow-up. Therefore, data during the four conditions were collapsed to create a single HR and RSA value per subject for the baseline (averaged over 98.0 ± 24 min time) and 2-year follow-up assessment (averaged over 101.3 ± 36 min time).

Consistency of HRV findings was checked using an alternative measure of (total) HRV, the standard deviation of normal-to-normal interval, which reflects both sympathetic and parasympathetic control.

Covariates

Sociodemographic information on age, gender, and education level was included.

Respiration rate has often been associated with HRV, and it has been suggested that research investigating HRV should take respiration rate into account (17). Health indicators (at both time points) were considered as covariates because these have been linked with depression and anxiety disorders and with ANS activity. Body mass

index was determined as measured weight in kilograms divided by the square of the measured height in meters. Physical activity was measured using the International Physical Activity Questionnaire (18) and expressed in MET-min per week (the multiple of one's resting metabolic rate times minutes of physical activity per week). Smoking status was defined as a categorical variable: nonsmoker, ex-smoker, and current smoker. Three categories were created for alcohol use: nondrinker, mild to moderate drinker (women: $\leq$ 2 glasses a day, men: $\leq$ 3 glasses a day), and heavy drinker (women: $>$ 2 glasses a day, men: $>$ 3 glasses a day). Self-reports were used for ascertainment of the presence of cardiovascular disease (including coronary disease, cardiac arrhythmia, angina, heart failure, and myocardial infarction) and other chronic conditions (epilepsy, diabetes, osteoarthritis, stroke, cancer, chronic lung disease, thyroid disease, liver disease, chronic fatigue syndrome, intestinal disorders, and ulcer). Furthermore, it was determined whether subjects were using beta-blocking agents (ATC code C07) or other cardiac medication (ATC codes C01, C02, C03, C04, C05, C08, and C09).

Clinical characteristics included severity of depressive symptoms, which was measured with the 30-item Inventory of Depressive Symptomatology (IDS) (19). Severity of anxiety symptoms was measured using the 21-item Beck Anxiety Inventory (BAI) (20). Severity scores were obtained at baseline and follow-up.

Statistical Analyses

Data were analyzed using SPSS 15.0. Characteristics at baseline and follow-up assessment were compared using paired *t* tests and McNemar statistics. Linear mixed-model analyses adjusted for all covariates at two time points were performed to first investigate whether ANS measures changed over time for the five disorder groups (fixed effect of group * time interaction). Second, to study whether HR and RSA changed when subjects started or stopped using an antidepressant, paired *t* tests were performed comparing ANS measures between baseline and follow-up for all 12 antidepressant groups. Because covariates can change within persons over a period of 2 years and these changes might influence ANS measures, we wanted to take possible changes in covariates into account when analyzing the longitudinal data. Therefore, adjusted linear mixed-model analyses were then conducted for the 2-year change scores for RSA and HR in the 12 antidepressant groups. Mixed-models analyses enable correction for time-varying covariates; correction for covariates at both baseline and follow-up is possible because it takes into consideration that these covariates were measured twice within the same person. Analyses were additionally corrected for depression and anxiety severity using the IDS and BAI scores.

If the fixed effect of the group by time interaction was significant, the change in RSA and HR within each of the groups was compared with the change in the persistent nonusers. To investigate whether discontinuing antidepressants resulted in a recovery of HR and RSA, analysis of covariance for repeated measures were performed, which investigated whether RSA and HR levels of subjects who discontinued antidepressants at follow-up were comparable to those of persistent nonusers. Effect sizes were calculated with Cohen *d*, defined as the difference in the means (or mean changes) of two groups, divided by the pooled standard deviation of these groups.

Results

Table 1 shows the main sample characteristics of all 2114 subjects at baseline and follow-up. Compared with baseline, subjects were more physically active, had a higher body mass index, smoked and drank less, used more beta blockers and other cardiac medication, and had more cardiovascular and other chronic diseases after 2 years (although the actual differences were generally modest). At follow-up, there were less healthy controls and less subjects had current psychopathology than at baseline. RSA slightly decreased, whereas HR and respiration rate increased over the 2-year follow-up period. Age was associated with RSA ($r = -.53$, $p < .001$) and HR ($r = .14$, $p < .001$), and women had higher RSA (8.1 msec) and HR (2.5 bpm) than men.

Linear mixed-model analyses adjusted for sociodemographics, health, and lifestyle factors showed that HR increased and RSA decreased for all anxiety/depression disorder groups from baseline to follow-up. There was no group by time interaction for HR ($F = .483$, $df = 4$, $p = .75$) or RSA ($F = 1.298$, $df = 4$, $p = .27$), indicating that changes in HR and RSA did not differ among persistent controls, subjects with a persistent current, or remitted diagnosis and subjects with new onset or remission of a disorder. Table 2 shows the mean uncorrected HR and RSA at baseline and follow-up for all 12 antidepressant use groups. Clearly, persistent antidepressant users and persistent nonusers did not display a major change in RSA (2-year changes $\leq$ 2.4 msec) or in HR (2-year changes $\leq$ 1.2 bpm), whereas RSA decreased remarkably in subjects who started using a TCA (-21.0 msec, $p = .04$), an SNRI (-15.3 msec, $p = .002$) or an SSRI (-8.2 msec, $p < .001$). HR increased when subjects started using a TCA or SNRI (2-year change for new TCA users: 5.8 bpm, $p = .09$ and for new SNRI users: 7.8 bpm, $p < .001$), but HR decreased for new SSRI users (-1.5 bpm, $p = .05$). RSA increased again in subjects who stopped using an antidepressant ($+$ 7.9 msec after SNRI use, $p = .001$, $+$ 7.5 msec after TCA use, $p = .27$ and $+$ 1.4 msec after SSRI use, $p = .27$) and HR decreased in subjects who stopped using TCAs or SNRIs (-2.8 bpm, $p = .30$ and $p < .001$, respectively).

Figure 1 shows the results of the fully adjusted mixed-model analyses on HR and RSA in the different antidepressant groups. The overall group by time interaction was significant for HR ($F = 9.274$, $df = 11$, $p < .001$) and RSA ($F = 7.461$, $df = 11$, $p < .001$), which indicates that changes in HR and RSA over time were significantly different across antidepressant groups taking into account all covariates. The 2-year decrease in RSA was minor among persistent nonusers (-1.1 msec). Subjects who started using an antidepressant, however, showed a significantly larger RSA decrease: new TCA users had a 2-year RSA decrease of 23 msec (compared with persistent nonusers: $t = 5.151$, $df = 1904$, $p < .001$, effect size $d = 1.487$), new SNRI users of 12 msec ($t = 3.470$, $df = 2087$, $p = .001$, $D = .724$) and new SSRI users of 7 msec ($t = 3.574$, $df = 2066$, $p < .001$, $d = .415$). Subjects switching from SNRIs to SSRIs gained in RSA (6 msec, $t = -1.955$, $df = 1988$, $p = .05$, $d = .515$), and the RSA of subjects switching from SSRIs to SNRIs decreased (7 msec, $t = 2.113$, $df = 2090$, $p = .04$, $d = .431$).

Analyses yielded similar but opposite findings for HR: whereas persistent nonusers only increased .5 bpm over 2 years, this increase was much larger for those who started the use of a TCA ($+$ 7 bpm, compared with persistent nonusers: $t = -3.076$, $df = 2086$, $p = .002$, $d = .899$) or SNRI ($+$ 8 bpm, $t = -4.572$, $df = 2086$, $p < .001$, $d = .934$), whereas SSRIs caused a minor but significant decrease in HR ($t = 2.495$, $df = 2087$, $p = .01$, $d = .271$). When subjects stopped using an antidepressant, a significant increase in RSA was seen: for TCA stoppers: $+$ 7 msec ($t = -2.011$, $df = 2080$, $p = .05$, $d = .529$), for SNRI stoppers: $+$ 7 msec ($t = -3.153$, $df = 1992$, $p = .002$, $d = .557$) and for SSRI stoppers: $+$ 2 msec ($t = -2.372$, $df = 2053$, $p = .02$, $d = .214$). Subjects switching from SNRIs to SSRIs showed a decrease HR (5 msec, $t = 2.526$, $df = 2030$, $p = .01$, $d = .799$) and the HR of subjects switching from SSRIs to SNRIs increased (9.5 msec, $t = -6.156$, $df = 2101$, $p < .001$, $d = 1.257$). Discontinuing use of TCAs or SNRIs decreased HR again (with 3 beats/min for both

Table 1. Sample Characteristics ($n = 2114$)

	Baseline	2-Year Follow-Up	%Δ	p^a
Sociodemographics				
Age, years (SD)	42.0 (13.1)			
% Female	66.2			
Education, years (SD)	12.4 (3.3)			
Health Factors				
Physical activity, 1000 MET min/week (SD)	3.7 (3.1)	4.1 (3.3)	10.8	<.001
Body mass index (SD)	25.4 (4.9)	25.7 (4.8)	1.2	<.001
Smoking, no./day (SD)	4.5 (8.3)	4.2 (7.9)	−6.7	<.001
Nonsmoker	615 (29.1)	657 (31.1)	6.9	<.001
Former smoker	741 (35.1)	739 (35.0)	−.3	
Current smoker	755 (35.8)	715 (33.9)	−5.3	
Alcohol use, drinks/day (SD)	1.03 (1.5)	.97 (1.4)	−5.8	<.001
Nondrinker, *n* (%)	327 (15.5)	361 (17.1)	10.3	.02
Mild/moderate drinker, *n* (%)	1535 (72.7)	1529 (72.4)	−.4	
Heavy drinker, *n* (%)	249 (11.8)	221 (10.5)	−11.0	
% use of beta blockers	160 (7.6)	178 (8.4)	10.5	.04
% use of other heart medication	226 (10.7)	278 (13.2)	23.4	<.001
% cardiovascular disease	139 (6.6)	177 (8.4)	27.3	<.001
Number of chronic diseases, mean (SD)	.89 (1.1)	.95 (1.1)	6.7	<.001
Psychopathologic Factors				
Control, *n* (% yes)	482 (22.8)	448 (21.2)	−7.0	<.001
Remitted diagnosis, *n* (% yes)	484 (22.9)	876 (41.5)	81.2	
Current diagnosis, *n* (% yes)	1145 (54.2)	787 (37.3)	−31.2	
Within current diagnosis				
Anxiety (% yes)	409 (35.7)	313 (39.8)	11.5	<.001
MDD (% yes).	278 (24.3)	202 (25.7)	5.8	
Comorbid diagnosis (% yes)	458 (40.0)	272 (34.6)	−13.5	
Autonomic Measures				
Respiratory sinus arrhythmia (msec, SD)	43.9 (24.8)	41.8 (22.3)	−4.8	<.001
Heart rate, beats/min (SD)	72.0 (9.7)	72.7 (9.7)	1.0	<.001
Respiration rate, breath per minute (SD)	17.1 (1.2)	17.3 (1.2)	1.2	<.001

FU, follow-up; MDD, major depressive disorder; MET, multiple of the resting metabolic rate.
[a]Comparison of baseline and follow-up values using paired *t* test (continuous variables) and McNemar statistics (dichotomous/categorical variable).

antidepressants, $t = 1.925$, $df = 2084$, $p = .05$, $d = .496$ and $t = 2.701$, $df = 2089$, $p = .007$, $d = .476$, respectively). Discontinuing use of an SSRI led to an increase HR of 3 beats/min ($t = -3.336$, $df = 2089$, $p = .001$, $d = .311$).

Adding the IDS and BAI scores of both time points as covariates did not change any of these results. Also, the pattern of results was similar with and without resting respiration rate added as a covariate.

To evaluate whether subjects who stopped using antidepressants did fully return to "normal" RSA and HR levels, we additionally compared their adjusted 2-year follow-up levels to those of persistent nonusers (Figure 2). At follow-up, the RSA levels of subjects who stopped using TCAs, SNRIs, and SSRIs were lower than the level observed among persistent nonusers, but only that of SSRI users reached significance ($p = .01$, $t = -2.552$, $df = 2087$, $d = .240$), presumably because of the small number of subjects in the TCA and SNRI groups. For HR levels, no significant differences could be observed at 2-year follow-up between persistent nonusers and subjects who had stopped taken an antidepressant of any of the three classes, although HR remained higher in subjects who stopped using a TCA ($p = .14$, $t = 1.479$, $df = 2091$, $d = .470$) and tended to become higher in the group that stopped SSRI use ($p = .06$, $t = 1.862$, $df = 2091$, $d = .175$).

Total HRV (standard deviation of normal-to-normal) showed almost identical patterns to HRV in the respiratory range, as did log transformed RSA (data not shown).

Discussion

The results of this study indicate that the use of antidepressants had a significant impact on HR and HRV. RSA, a measure of HRV reflecting cardiac vagal control, was considerably lowered in subjects who had started a TCA, SNRI, or SSRI compared with subjects who did not change in antidepressant use (persistent users and persistent nonusers). TCAs had the strongest effect, followed by SNRIs and SSRIs. In contrast, discontinuing antidepressant use systematically increased cardiac vagal control. In keeping with the unfavorable effects on cardiac vagal control, HR was significantly increased by the use of TCAs or SNRIs. In SSRI users, lowered RSA was accompanied by a mild decrease in HR, suggesting a parallel beneficial effect of SSRIs on sympathetic cardiac control. Importantly, no underlying effects of changes in depression or anxiety disorders were found: similar patterns of 2-year changes in RSA and HR were observed for healthy control subjects, persons who developed a new disorder, or persons who remitted from a disorder. In addition, changes in ANS measures over time in different antidepressant groups were not explained by improvement of symptoms (e.g., due to use of a specific antidepressant) because additional correction for IDS and BAI scores on both time points did not alter our findings.

These longitudinal findings strengthen previous cross-sectional findings, suggesting unfavorable effects of antidepressants on autonomic function that were independent of current or past depres-

Table 2. Mean Respiratory Sinus Arrhythmia (RSA) and Heart Rate (HR) at Baseline and Follow-Up for the Antidepressant Groups

Antidepressant Use at Baseline	Antidepressant Use at Follow-Up	*n*	RSA at Baseline, msec (SD)	RSA at Follow-Up, msec (SD)	Δ msec	t^a	p^a	Cohen's *d*	HR Baseline, bpm (SD)	HR follow-up, bpm (SD)	Δ bpm	t^a	p^a	Cohen's *d*
No	No	1511	46.4 (25.7)	44.3 (22.9)	−2.1	5.174	<.001	.086	71.8 (9.5)	72.3 (9.5)	.5	−2.868	.004	.053
No	TCA	12	42.8 (32.7)	19.7 (12.4)	−23.1	2.294	.04	.934	74.1 (8.7)	80.4 (11.5)	5.8	−1.770	.09	.618
TCA	No	10	27.2 (16.1)	34.7 (19.5)	7.5	−1.184	.27	.419	78.8 (6.7)	76.0 (7.2)	−2.8	1.104	.30	.403
TCA	TCA	35	18.3 (9.5)	18.5 (9.3)	.2	−.188	.85	.021	83.6 (12.6)	83.2 (11.1)	−.3	.300	.77	.034
No	SNRI	23	51.7 (28.2)	36.4 (18.6)	−15.3	3.558	.002	.641	70.0 (11.5)	77.8 (9.5)	7.8	−4.481	<.001	.740
SNRI	No	32	31.9 (14.6)	38.8 (19.3)	7.9	−3.599	.001	.403	73.1 (9.2)	70.5 (8.0)	−2.6	1.932	.06	.302
SNRI	SSRI	10	40.8 (23.8)	45.6 (28.6)	4.8	−.881	.40	.182	74.7 (10.3)	69.8 (10.0)	−4.9	2.330	.05	.483
SNRI	SNRI	65	29.9 (14.8)	27.5 (13.2)	−2.4	1.813	.08	.171	75.0 (9.5)	76.2 (10.4)	1.2	−1.464	.15	.120
No	SSRI	74	49.6 (25.9)	41.4 (20.5)	−8.2	4.056	<.001	.351	71.3 (9.0)	69.8 (8.4)	−1.5	1.996	.05	.172
SSRI	No	123	40.7 (20.7)	42.1 (20.7)	1.4	−1.098	.27	.068	71.4 (8.9)	74.3 (10.4)	2.9	−4.093	<.001	.300
SSRI	SNRI	24	35.1 (17.7)	26.4 (13.1)	−8.7	2.514	.02	.559	69.2 (13.2)	79.3 (11.5)	10.1	−4.827	<.001	.816
SSRI	SSRI	195	36.7 (17.9)	36.3 (17.9)	−.4	.572	.57	.022	70.8 (9.7)	71.5 (9.0)	.7	−1.599	.11	.075
Total		2114												

SNRI, serotonergic and noradrenergic working antidepressant; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant.
[a]Based on paired *t* tests between baseline and 2-year follow-up values of RSA and HR. *p* values are for illustrative purposes only and are uncorrected for multiple testing.

sive or anxiety disorders (1,6). The hypothesis that depression or anxiety disorders cause cardiovascular disease (CVD) (21–28) by dysregulating the autonomic nervous system is therefore not supported by our findings. Instead, our results suggest that the antidepressant use inherent in having these disorders could explain part of the link between depression/anxiety and the development of CVD. We hasten to add that this is a hypothesis only. Perhaps the unfavorable autonomic effects of antidepressants are amply balanced by the beneficial effects of a successful improvement of mood. In addition, the effects of SSRIs on HR may imply beneficial effects on sympathetic activity that could counter the negative effects on parasympathetic activity and protect against CVD. Overall, the current evidence for the effects of various antidepressants for CVD risk is heterogeneous (especially for SSRI), with studies indicating beneficial as well as detrimental effects (29–40).

The mechanisms through which antidepressants exert their effects on parasympathetic control over the heart remain incompletely understood. At the brainstem level, serotonin reuptake inhibition may influence various relay nuclei of the parasympathetic nervous system (41–45) (40). The lowered RSA seen in our study may reflect a decrease in net cardiac vagal effects resulting from these serotonergic effects on vagal activity. The decrease in HR seen in SSRI users may be caused by a parallel decrease in sympathetic effects because effects of norepinephrine clearance have been described for some serotonin receptors (46–50). In keeping with this,

Figure 1. Mean differences in respiratory sinus arrhythmia (RSA) and heart rate between baseline and follow-up for the antidepressant groups. *$p \leq .05$, **$p \leq .01$, ***$p \leq .001$; *p* values are based on comparison of mean change with that of the persistent nonuser group. SNRIs, serotonergic and noradrenergic antidepressants; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

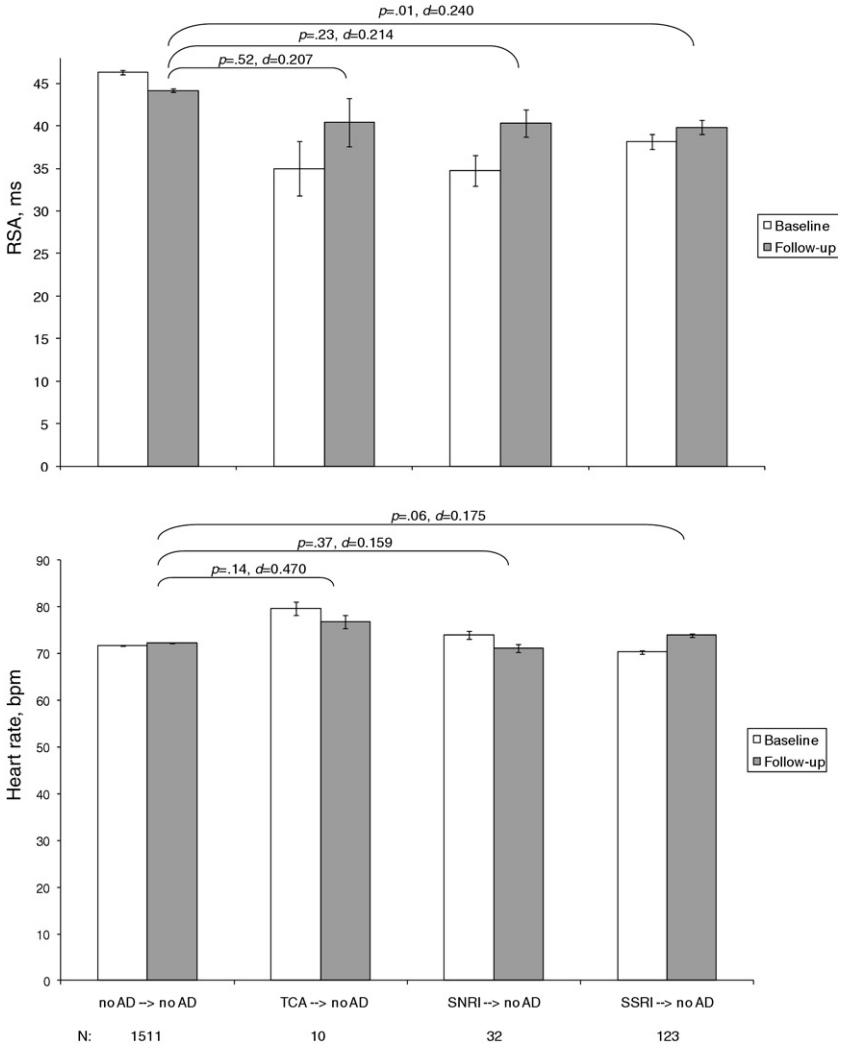

Figure 2. Mean respiratory sinus arrhythmia (RSA) and heart rate for the persistent nonusers and the groups that stopped using an antidepressant. AD, antidepressant; SNRIs, serotonergic and noradrenergic antidepressants; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants. *p* values are based on comparison of follow-up values with that of the persistent nonusers.

Barton *et al.* (2007) found a significant decrease in the sympathetic nervous system tone after SSRI use as measured by cardiac norepinephrine spillover (3). In contrast, the antivagal effects of TCAs and SNRIs may occur largely in the heart itself. Both types of antidepressants inhibit the reuptake of norepinephrine, causing a major increase in norepinephrine in the synaptic cleft. The effects of this on the sinoatrial adrenoceptors may not only increase HR directly (51,52) but also decrease acetylcholinergic effects on the pacemaker cells by the principles of accentuated antagonism (53–57).

We acknowledge some limitations of our study. Although the subjects in this longitudinal study served as their own controls and a pseudo-experimental setup was created, we acknowledge that no actual experimental design was used. Because subjects were not randomized to a specific antidepressant group, other clinical factors might have directed them to start or stop using specific antidepressants. However, because new users of antidepressants had similar baseline RSA and HR levels as persistent nonusers, there does not seem to be a baseline difference between subjects who do and do not start using an antidepressant. Consequently, it seems unlikely that underlying factors caused the changes in autonomic activity found in our study. Another limitation is the small number of subjects in groups of medication switchers, especially in TCA use. Although major changes in RSA were seen in TCA switching groups, results did not reach significance, probably because of these small numbers. In addition, group sizes might have contributed to the variance between these groups, and results should be interpreted with care. We also point out that we used basal values of HR and HRV only. A number of studies have suggested that it is specifically HR (or HRV) reactivity to an acute stressor that is associated with psychopathology (58,59).

This study had several strengths as well. For instance, the longitudinal setup made it possible to investigate the effects of 2-year changes in antidepressant use, providing strong evidence for causal inference. In addition, the large sample size enabled us to investigate the contribution of different antidepressants and consider an extensive range of longitudinal covariates.

In conclusion, our longitudinal findings provide support for a causal, lowering effect of all antidepressants (TCA, SSRI, and SNRI) on cardiac vagal control and imply that TCAs and SNRIs cause an increase in HR. Clinicians are advised to contemplate the possible effects on autonomic nervous activity because these effects have been shown to be associated with increased blood pressure and other metabolic abnormalities, such as unfavorable lipid profiles and high glucose levels (60). Fortunately, we also observed that the unfavorable effects on autonomic nervous system function appear to be partly reversible because stopping antidepressants shifted ANS indicators in the direction of normal values.

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