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Longitudinal Evidence for Unfavourable effects of Antidepressants on Heart Rate Variability

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ABSTRACT

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

Methods: Longitudinal data was obtained in the Netherlands Study of Depression and Anxiety (NESDA). At baseline and 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 to continuous non-users, subjects who started the use of a tricyclic antidepressant or a serotonergic and noradrenergic working antidepressant showed a significantly greater increase in heart rate and decrease of respiratory sinus arrhythmia in 2 years. Subjects who started the use of selective serotonin re-uptake inhibitors also showed a decrease in RSA, but their heart rate did not increase. Discontinuing antidepressants systematically caused opposite effects; levels returned in direction of levels observed among non-users.

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 unfavourable effects are (partly) reversible.

INTRODUCTION

Recent research has indicated a potential important role of antidepressants use in the dysregulation of the autonomic nervous system (ANS) that has been observed among depressed or anxious subjects[1-9]. In these subjects, the use of tricyclic antidepressants (TCAs), serotonergic and noradrenergic working antidepressants (SNRIs) and selective serotonin re-uptake inhibitors (SSRIs) was associated with increased heart rate and decreased heart rate variability, whereas associations were small or even non-significant when heart rate and heart rate variability were compared between antidepressant naive depressed or anxious subjects and healthy controls[1,5,10]. These results imply that depression and anxiety disorders itself did not cause diminished parasympathetic nervous system (PNS) and increased sympathetic nervous system (SNS) activity, but that this effect might be driven by the effects of antidepressants. Nevertheless, previous studies were of cross-sectional nature, 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 heart rate and heart rate variability. It also examined whether discontinuation of antidepressants results in recovery of autonomic measures to levels seen among non-users. The large sample size enabled us to consider important covariates and address various antidepressants classes (TCAs, SNRIs, and SSRIs).

METHODS

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 North European ancestry) to examine the long-term course of depression and anxiety disorders. The rationale,

methods and recruitment strategy have been described elsewhere[11]. 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 different locations in the Netherlands in various settings: in general community, through a screening procedure in primary care, and through mental health care organizations. The baseline assessment lasted four hours on average and included assessment of demographic, health, and lifestyle characteristics, a standardized diagnostic psychiatric interview and a medical assessment. The research protocol was approved by the Ethical Committee of 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). Non-responders were younger, more often of non-northern European ancestry, less educated, and more often had major depressive disorder (MDD)[12].

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 (CIDI, World Health Organization, version 2.1). The CIDI establishes diagnoses according to the DSM-IV criteria[13] and has shown high inter-rater and test- retest reliability, as well as high validity for depressive and anxiety disorder[14]. 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 - a remitted (longer than six months ago) 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 a 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 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 based on drug container inspection for all drugs used in the month before assessment and classified according to the Anatomical Therapeutic Chemical (ATC) classification[15]. Use of antidepressants was considered present when taken for at least one month and 50% of the time, and included TCAs (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 non-users, 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 of antidepressant 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 ten subjects (e.g. those who switched from TCAs to SSRIs). Another 22 subjects were excluded because they had other psychiatric diagnosis (such as dysthymia or minor depression) in absence of a MDD or anxiety diagnosis. In addition, 428 subjects had missing physiological data at baseline or follow-up. Consequently, data from 2114 subjects were categorized into twelve antidepressant groups: persistent non-users (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).

Physiological measurement

Basal respiratory sinus arrhythmia (RSA), an index of cardiac vagal control, and heart rate, an index of combined PNS and SNS 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 (ECG) and changes in thorax impedance (dZ) from six electrodes placed at chest and back of the subjects[16,17]. An automatic scoring

algorithm detected the beginning and end of inspiration and expiration in the respiration signal obtained from the filtered (0.1–0.4 Hz) dZ signal. Respiratory sinus arrhythmia was assessed by peak-valley estimation (pvRSA) using the combined ECG and respiration signals. Per breath, estimates of pvRSA were obtained by subtracting the shortest inter-beat-interval during heart rate acceleration in the inspirational phase from the longest inter-beat-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, who maintain full freedom of movement, tend to habituate very 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 where subjects were non-stationary. Removal of breaks and non-stationary parts (~ 15 minutes) resulted in four conditions: a supine rest condition with blood pressure measurement (baseline: 9.8 ± 3.0 minutes, follow-up: 9.4 ± 3.0 minutes), and three conditions with mild cognitive load in which the subjects were sitting upright: interview session I (baseline: 37.8 ± 12.3 minutes, follow-up: 46.0 ± 25.9 minutes), interview session II (baseline: 35.8 ± 12.8 minutes, follow-up: 32.5 ± 12.0 minutes) and a computer task (The Implicit Association Task baseline: 16.0 ± 3.8 minutes, follow-up: 15.2 ± 3.4 minutes). 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[18], 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 one single heart rate and RSA value per subject for the baseline (averaged over 98.0 ± 24 minutes time) and 2-year follow-up assessment (averaged over 101.3 ± 36 minutes time).

Consistency of heart rate variability findings was checked using an alternative measure of (total) heart rate variability: The standard deviation of normal-to-normal interval (SDNN), which reflects both sympathetic and parasympathetic control.

Covariates

Sociodemographic information on age, gender and educational level was included. Respiration rate has often been associated with heart rate variability and it is suggested that research investigating heart rate variability should take respiration rate into account[19]. Health indicators (at both time points) were considered as covariates since these have been linked with both depression and anxiety disorders and ANS activity. Body mass index (BMI) 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[20] and expressed in MET-minutes 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: non-smoker, ex-smokers, and current smokers. Three categories were created for alcohol use: Non-drinker, mild to moderate drinker (women: ≤ 2 glasses a day, men: ≤ 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, Rush *et al*. 1996[21]). Severity of anxiety symptoms was measured using the 21-item Beck Anxiety Inventory (BAI, Beck *et al*. 1988[22]). Severity scores were obtained at baseline and follow-up.

Statistical analyses

Data was 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 by time interaction). Second, to study whether heart rate 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 two 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 heart rate 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 since 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 group by time interaction was significant, the change in RSA and heart rate within each of the groups was compared to the change in the persistent non-users. To investigate whether stopping the use of antidepressants resulted in a recovery of heart rate and RSA, analysis of covariance for repeated measures were performed, which investigated whether RSA and heart rate levels of subjects who discontinued antidepressants at follow-up were comparable to those of persistent non-users. 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 to baseline, subjects were more physically active, had a higher BMI, smoked and drank less (often), used more beta-blockers and other cardiac medication, and had more cardiovascular and other chronic diseases after two years (although the actual differences were generally modest). At follow-up, there were less healthy controls and fewer subjects had current psychopathology than at baseline. RSA slightly decreased, whereas heart rate and respiration rate increased over the 2-year follow-up period. Age was associated with RSA (r=-0.53, p<.001), and heart rate (r=0.14, p<.001) and women had higher RSA (8.1 ms) and heart rate (2.5 bpm) than men.

Linear mixed-model analyses adjusted for sociodemographics, health and lifestyle factors showed that heart rate increased and RSA decreased for all anxiety/depression disorder groups from baseline to follow-up. There was no

group by time interaction for heart rate (F=0.483, df=4, p=.75) or RSA (F=1.298, df=4, p=.27), indicating that changes in heart rate and RSA did not differ between persistent controls, subjects with a persistent current or remitted diagnosis and subjects with new onset or remission of a disorder.

Table 1. Sample Characteristics

	Participants (n=2114), %			
	Baseline	2 year follow-up	%Δ	p[a]
Sociodemographics				
Age, mean (SD), years	42.0 (13.1)			
Female sex	66.2			
Education, mean (SD), years	12.4 (3.3)			
Health Factors				
Physical activity, mean (SD), 1000 MET min/week	3.7 (3.1)	4.1 (3.3)	10.8	<.001
Body Mass Index, mean (SD), kg/m2	25.4 (4.9)	25.7 (4.9)	1.2	<.001
Smoking, mean, (SD), No./day	4.5 (8.3)	4.2 (7.9)	-6.7	<.001
Non-smoker	29.1	31.1	6.9	
Former smoker	35.1	35.0	-0.3	<.001
Current smoker	35.8	33.9	-5.3	
Alcohol use, mean (SD), drinks/day	1.03 (1.5)	0.97 (1.4)	-5.8	<.001
Non drinker	15.5	17.1	10.3	
Mild/moderate drinker	72.7	72.4	-0.4	.02
Heavy drinker	11.8	10.5	-11.0	
Use beta-blockers	7.6	8.4	10.5	.04
Use other heart medication	10.7	13.2	23.4	<.001
Cardiovascular disease	6.6	8.4	27.3	<.001
Number of chronic diseases, mean (SD), No.	0.89 (1.1)	0.95 (1.1)	6.7	<.001
Psychopathological Factors				
Control	22.8	21.2	-7.0	
Remitted diagnosis	22.9	41.5	81.2	<.001
Current diagnosis	54.2	37.3	-31.2	
Within current diagnosis				
Anxiety	35.7	39.8	11.5	
Major Depressive Disorder	24.3	25.7	5.8	<.001
Comorbid Diagnosis	40.0	34.6	-13.5	
Autonomic Measures				
Respiratory Sinus Arrhythmia, mean (SD), ms	43.9 (24.8)	41.8 (22.3)	-4.8	<.001
Heart rate, mean (SD), beats per minute	72.0 (9.7)	72.7 (9.7)	1.0	<.001
Respiration rate, mean (SD), breaths/min	17.1 (1.2)	17.3 (1.2)	1.2	<.001

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 variables)

Table 2 shows the mean uncorrected heart rate and RSA at baseline and follow-up for all 12 antidepressant use groups. Clearly, persistent antidepressant users and persistent non-users did not display a major change in RSA (2-year changes ≤2.4 ms) or in heart rate (2-year changes ≤1.2 bpm), whereas RSA decreased remarkably in subjects who started using a TCA (-21.0 ms, p=.04), an SNRI (-15.3 ms, p=.002) or an SSRI (-8.2 ms, p<.001). Heart rate 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 heart rate decreased for new SSRI users (-1.5 bpm, p=.05). RSA increased again in subjects who stopped using an antidepressant (+7.9 ms after SNRI use, p=.001, + 7.5ms after TCA use, p=.27 and +1.4 ms after SSRI use, p=.27) and heart rate 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 heart rate and RSA in the different antidepressant groups. The overall group by time interaction was significant for heart rate (F=9.274, df=11, p<.001) and RSA (F=7.461, df=11, p<.001), which indicates that changes in heart rate 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 non-users (-1.1 ms). Subjects who started using an antidepressant, however, showed a significantly larger RSA decrease: new TCA users had a 2-year RSA decrease of 23 ms (compared with persistent non-users: t=5.151, df=1904, p<.001, effect size d=1.487), new SNRI users of 12 ms (t=3.470, df=2087, p=.001, d=0.724) and new SSRI users of 7 ms (t=3.574, df=2066, p<.001, d=0.415). Subjects switching from SNRIs to SSRIs gained in RSA (+6 ms, t=-1.955, df=1988, p=.05, d=0.515) and the RSA of subjects switching the other way around decreased (-7 ms, t=2.113, df=2090, p=.04, d=0.431).

Analyses yielded similar but opposite findings for heart rate: whereas persistent non-users only increased 0.5 bpm over two years, this increase was much larger for those who started the use of a TCA (+7 bpm, compared with persistent non-users: t=-3.076, df=2086, p=.002, d=0.899) or SNRI (+8 bpm, t=-4.572, df=2086, p<.001, d=0.934), whereas SSRIs caused a minor but significant decrease in heart rate (t=2.495, df=2087, p=.01, d=0.271). When subjects stopped using an antidepressant, a significant increase in RSA was seen: for TCA stoppers: +7 ms (t=-2.011, df=2080, p=.05, d=0.529), for SNRI stoppers: +7 ms (t=-3.153, df=1992, p=.002, d=0.557) and for SSRI stoppers: +2 ms (t=-2.372, df=2053, p=.02, d=0.214). Subjects switching from SNRIs to SSRIs showed a decrease in heart rate (-5 ms,

Table 2. Mean RSA and Heart Rate at Baseline and at Follow-up for the Different Antidepressant Groups

AD use at BL	AD use at FU	N	RSA BL, ms (SD)	RSA FU, ms (SD)	Δ ms	t^a	p^a	*d*	Heart rate BL, bpm (SD)	Heart rate FU, bpm (SD)	Δ bpm	t^a	p^a	*d*
No	No	1511	46.4 (25.7)	44.3 (22.9)	-2.1	5.174	<.001	0.086	71.8 (9.5)	72.3 (9.5)	0.5	-2.868	.004	0.053
No	TCA	12	42.8 (32.7)	19.7 (12.4)	-23.1	2.294	.04	0.934	74.1 (8.7)	80.4 (11.5)	5.8	-1.770	.09	0.618
TCA	No	10	27.2 (16.1)	34.7 (19.5)	7.5	-1.184	.27	0.419	78.8 (6.7)	76.0 (7.2)	-2.8	1.104	.30	0.403
TCA	TCA	35	18.3 (9.5)	18.5 (9.3)	0.2	-0.188	.85	0.021	83.6 (12.6)	83.2 (11.1)	-0.3	0.300	.77	0.034
No	SNRI	23	51.7 (28.2)	36.4 (18.6)	-15.3	3.558	.002	0.641	70.0 (11.5)	77.8 (9.5)	7.8	-4.481	<.001	0.740
SNRI	No	32	31.9 (14.6)	38.8 (19.3)	7.9	-3.599	.001	0.403	73.1 (9.2)	70.5 (8.0)	-2.6	1.932	.06	0.302
SNRI	SSRI	10	40.8 (23.8)	45.6 (28.6)	4.8	-0.881	.40	0.182	74.7 (10.3)	69.8 (10.0)	-4.9	2.330	.05	0.483
SNRI	SNRI	65	29.9 (14.8)	27.5 (13.2)	-2.4	1.813	.08	0.171	75.0 (9.5)	76.2 (10.4)	1.2	-1.464	.15	0.120
No	SSRI	74	49.6 (25.9)	41.4 (20.5)	-8.2	4.056	<.001	0.351	71.3 (9.0)	69.8 (8.4)	-1.5	1.996	.05	0.172
SSRI	No	123	40.7 (20.7)	42.1 (20.7)	1.4	-1.098	.27	0.068	71.4 (8.9)	74.3 (10.4)	2.9	-4.093	<.001	0.300
SSRI	SNRI	24	35.1 (17.7)	26.4 (13.1)	-8.7	2.514	.02	0.559	69.2 (13.2)	79.3 (11.5)	10.1	-4.827	<.001	0.816
SSRI	SSRI	195	36.7 (17.8)	36.3 (17.9)	-0.4	0.572	.57	0.022	70.8 (9.7)	71.5 (9.0)	0.7	-1.599	.11	0.075
Total		2114												

AD, antidepressant; BL, baseline; FU, follow-up; RSA, respiratory sinus arrhythmia; SNRI, serotonergic and noradrenergic working antidepressant; SSRI, selective serotonin re-uptake inhibitors; TCA, tricyclic antidepressant.

[a] Based on paired t-tests between baseline and 2-year follow-up values of RSA and heart rate. These p-values are for illustrative purposes only and are uncorrected for multiple testing

t=2.526, *df*=2030, *p*=.01, *d*=0.799) and the heart rate of subjects switching from SSRIs to SNRIs increased (+9.5 ms, *t*=-6.156, *df*=2101, *p*<.001, *d*=1.257). Discontinuing use of TCAs or SNRIs decreased heart rate again (with 3 beats per minute for both antidepressants, *t*=1.925, *df*=2084, *p*=.05, *d*=0.496 and *t*=2.701, *df*=2089, *p*=.007, *d*=0.476, respectively). Stopping the use of a SSRI led to an increase in heart rate of 3 beats per minute (*t*=-3.336, *df*=2089, *p*=.001, *d*=0.311).

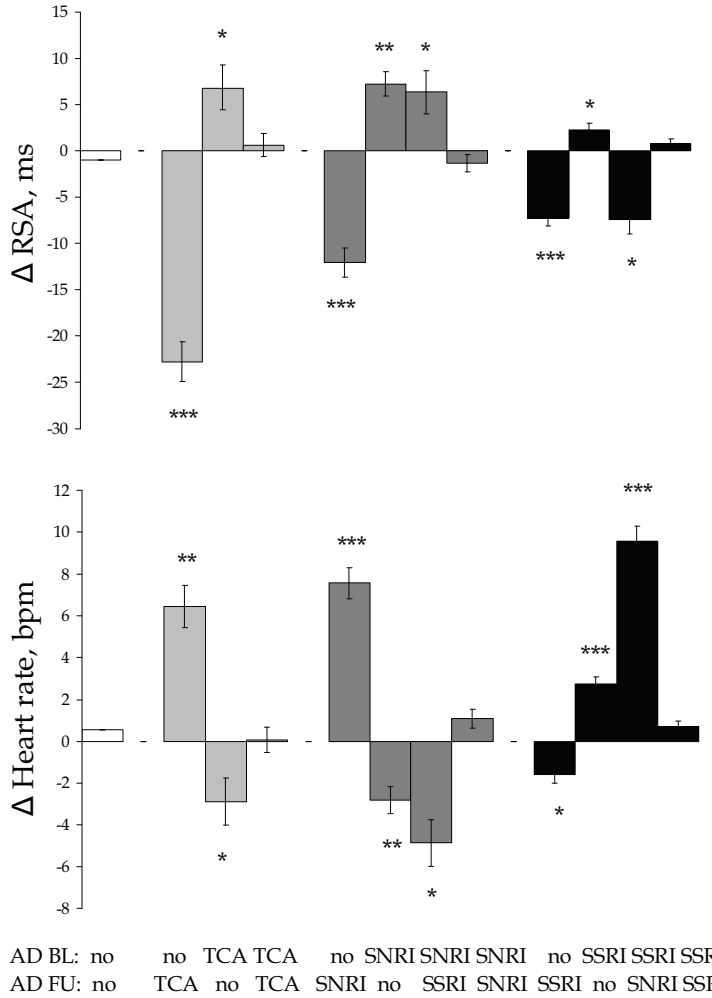

Figure 1. *Mean differences in RSA and heart rate between baseline and follow-up for different antidepressant groups. P-values are based on comparison of mean change with that of the persistent non-user group. * p≤.05 ** p≤.01 *** p≤.001*

Adding the IDS and BAI scores of both time points as covariates did not change any of the above-mentioned 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 heart rate levels, we additionally compared their adjusted 2-year follow-up levels to those of persistent non-users (**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 non-users, but only that of SSRI users reached significance (*p*=.01, *t*=-2.552, *df*=2087, *d*=0.240), presumably because of the small number of subjects in the TCA and SNRI groups. For heart rate levels, no significant differences could be observed at 2-year follow-up between persistent non-users and subjects who had stopped taking an antidepressant of any of the three classes, although heart rate remained higher in

subjects who stopped using a TCA (p=.14, t=1.479, df=2091, d=0.470) and tended to become higher in the group that stopped SSRI use (p=.06, t=1.862, df=2091, d=0.175).

Total heart variability (SDNN) showed almost identical patterns to heart rate variability in the respiratory range, as did log transformed RSA (data not shown).

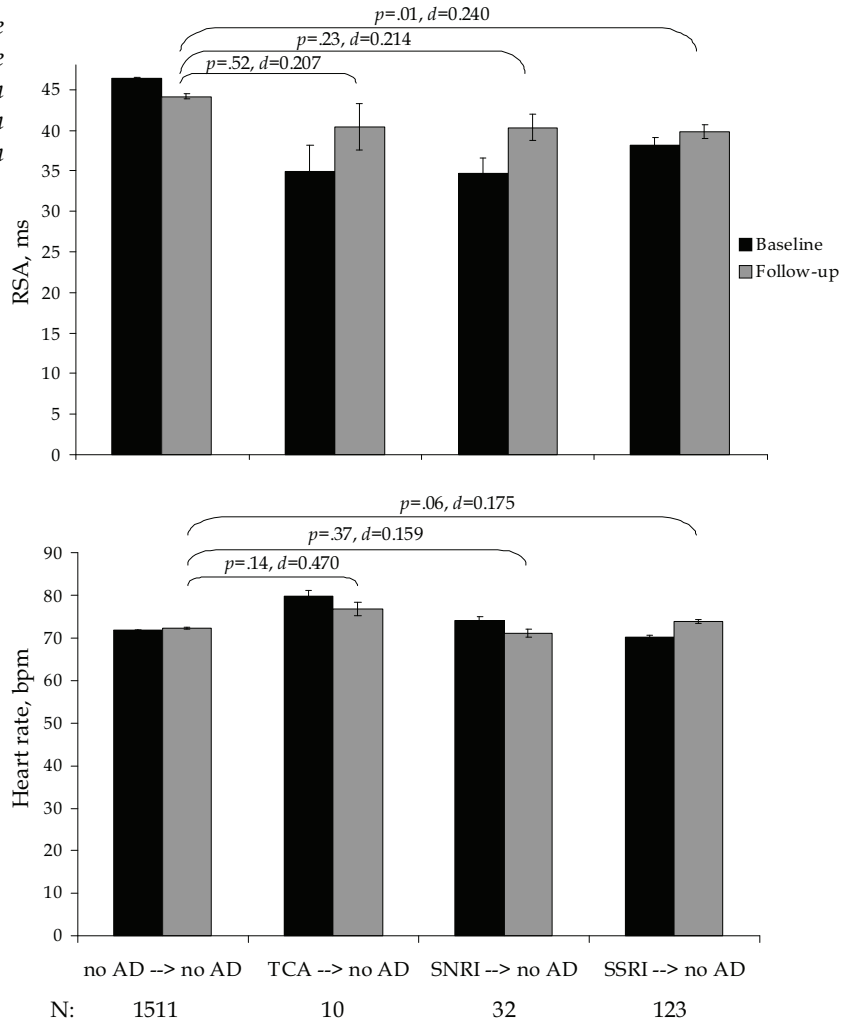

Figure 2. *Mean RSA and heart rate for the persistent non-users and the groups that stopped using an antidepressant. P-values are based on comparison of follow-up values with that of the persistent non-users*

DISCUSSION

The results of this study indicate that the use of antidepressants had a significant impact on heart rate and heart rate variability. RSA, a measure of heart rate variability reflecting cardiac vagal control, was considerably lowered in subjects who had started the use of a TCA, SNRI, or SSRI compared to subjects

who did not change in antidepressant use (persistent users and persistent non-users). TCAs had the strongest effect, followed by SNRIs and SSRIs. In contrast, discontinuing the use of an antidepressant systematically increased cardiac vagal control. In keeping with the unfavourable effects on cardiac vagal control, heart rate was significantly increased by the use of TCAs or SNRIs. In SSRI users, lowered RSA was accompanied by a mild decrease in heart rate, 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 heart rate were observed for healthy controls, 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 the use of an antidepressant), since 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 unfavourable effects of antidepressants on autonomic function that were independent of current or past depressive or anxiety disorders[1,6]. The hypothesis that depression and anxiety disorders cause cardiovascular diseases (CVD[23-30]) 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 has the status of a hypothesis only. It is possible that the unfavourable autonomic effects of antidepressants are amply balanced by the beneficial effects of a successful improvement of mood. In addition, the effects of SSRIs on heart rate may imply beneficial effects on sympathetic activity that might counter the negative effects on parasympathetic activity and protect against CVD. Overall, the current evidence for the effects of different antidepressants on CVD risk is heterogeneous (especially for SSRI) with studies indicating beneficial as well as detrimental effects[31-42].

The mechanisms by which the antidepressants exert their effects on parasympathetic control over the heart remain incompletely understood. At the brainstem level, serotonin re-uptake inhibition may influence various relay nuclei of the parasympathetic nervous system[43-47]. The lowered RSA seen in the present study may reflect a decrease in net cardiac vagal effects resulting from these serotonergic effects on vagal activity. The decrease in heart rate seen in SSRI users

may be caused by a parallel decrease in sympathetic effects, since effects of norepinephrine (NE) clearance have been described for some serotonin receptors[48-52]. In keeping, Barton *et al*. (2007) found a significant decrease in the SNS tone after SSRI use as measured by cardiac NE spillover[3]. In contrast, the anti-vagal effects of TCAs and SNRIs may occur largely in the heart itself. Both types of antidepressants inhibit the re-uptake of NE, causing a major increase in NE in the synaptic cleft. The effects of this additional NE on the sinoatrial adrenoceptors may not only increase heart rate directly[53,54] but also decrease acetylcholinergic effects on the pacemaker cells by the principles of accentuated antagonism[55-59].

Some limitations of our study have to be acknowledged. 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 subjects to start or stop using specific antidepressants. However, since new users of antidepressants had similar baseline RSA and heart rate levels as persistent non-users, 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 further have to point out that we used basal values of heart rate and heart rate variability only. A number of studies have suggested that it is specifically heart rate (variability) reactivity to an acute stressor that is associated with psychopathology[60,61].

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 heart rate. Clinicians would be well-advised to contemplate on the possible effects on autonomic

nervous activity, since these have shown to be associated with increased blood pressure and other metabolic abnormalities such as unfavourable lipid profile and high glucose levels[62]. Fortunately, we also observed that the unfavourable effects on autonomic nervous system function appears to be partly reversible since stopping antidepressants shifted autonomic nervous system indicators in the direction of 'normal' values.

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