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RESEARCH ARTICLE

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# Heart rate variability as a biomarker of anxious depression response to antidepressant medication

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**Background:** There is a need to identify biomarkers of treatment outcomes for major depressive disorder (MDD) that can be disseminated. We investigated the predictive utility of pretreatment heart rate variability (HRV) for outcomes of antidepressant medication in MDD, with pretreatment anxious depression as a hypothesized moderator of HRV effects.

**Methods:** A large, randomized, multicenter practical trial (International Study to Predict Optimized Treatment in Depression) in patients with current nonpsychotic MDD ($N$ = 1,008; 722 completers) had three arms: escitalopram, sertraline, and venlafaxine-extended release. At pretreatment, patients were defined as having anxious ($N$ = 309) versus nonanxious ($N$ = 413) depression and their resting high-frequency HRV (root mean square of successive differences) was assessed. Patients' usual treating clinicians managed medication. At 8 weeks, primary outcomes were clinician-rated depressive symptom response and remission; secondary outcomes were self-reported response and remission.

**Results:** Pretreatment HRV predicted antidepressant outcomes as a function of anxious versus nonanxious depression. In anxious depression, patients with higher HRV had better outcomes, whereas patients with lower HRV had poorer outcomes. In nonanxious depression, patients with lower HRV had better outcomes, whereas patients with higher HRV had poorer outcomes. Some simple effects were not significant. Results did not differ by treatment arm and remained significant when controlling for important covariates.

**Conclusions:** These findings inform a precision medicine approach in which clinical and biological assessments may be integrated to facilitate treatment outcome prediction. Knowing about HRV may help determine which patients with anxious depression could benefit from antidepressants and which patients may require a different treatment approach.

KEYWORDS
antidepressant, anxious depression, depression, heart rate variability, outcome, treatment

## 1 | INTRODUCTION

Major depressive disorder (MDD) places an enormous burden on society worldwide (World Health Organization, 2017). Depressive disorders are the second leading cause of years lost to disability (Ferrari et al., 2013) and, among mental disorders, have the highest population attributable risk for all-cause mortality (Walker, McGee, & Druss, 2015). Furthermore, the costs of treating MDD are substantial: in the United States, the direct medical costs for patients diagnosed with MDD totaled $99 billion in 2010, a sharp rise from $26 billion in 2000 (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015). Antidepressant medications have been utilized increasingly as a front-line treatment for depression; however, only one-third to one-half of patients with MDD who complete an initial course of antidepressants achieve remission (Saveanu et al., 2015; Trivedi et al., 2006).

These alarming statistics have hastened efforts to identify predictors of treatment outcomes in MDD (Kemp, Gordon, Rush, & Williams, 2008). Although in general clinical variables have not been powerful predictors, across several studies anxious depression at pretreatment has been found to predict poorer response to antidepressants. For example, in the STAR*D trial, anxious depression (Hamilton Rating Scale for Depression [$HRSD_{17}$] anxiety/somatization subscale score $\geq$ 7) predicted a lower rate of remission with citalopram and, upon switching medications, lower rates of remission with sustained-release bupropion, sertraline, and venlafaxine extended-release (venlafaxine-XR; Fava et al., 2008). While poorer outcomes

  

for anxious than for nonanxious depression have since been replicated with a variety of antidepressants (Domschke, Deckert, Arolt, & Baune, 2010; Papakostas & Larsen, 2011), the evidence is not fully consistent (Nelson, 2008; Uher et al., 2011). Recently, in the International Study to Predict Optimized Treatment in Depression (iSPOT-D; Williams et al., 2011), we did not find any significant associations between anxious depression and acute remission rates across treatment with escitalopram, sertraline, and venlafaxine-XR (Arnow et al., 2015).

Incorporating biomarkers to predict treatment outcomes holds promise, and there is a need to identify metrics that can be disseminated cost-effectively (Kemp et al., 2008). Cardiac measures, including heart rate (HR) and heart rate variability (HRV), are acquired in many routine health care practices. High-frequency (HF)-HRV quantifies beat-to-beat fluctuations in HR that are largely due to parasympathetic control. Relatively higher resting HF-HRV is theorized to reflect adaptive functioning (Porges, 1995); accumulating evidence supports a model in which HF-HRV indexes neural activity in the prefrontal cortex associated with emotional, cognitive, and autonomic regulation (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012).

Given the dysregulation of emotional, cognitive, and autonomic functions in MDD, HF-HRV is a relevant metric to consider for treatment prediction. In a meta-analysis of 18 studies, individuals diagnosed with MDD were found to have lower resting levels of HF-HRV than did nonpsychiatric controls (Kemp et al., 2010). However, some studies reported no significant differences in HF-HRV between MDD and control participants (e.g., Licht et al., 2008), and the overall effect size appears small (Rottenberg, 2007). In some cases, antidepressant use, rather than depression per se, was found to be associated with reduced HRV (Kemp et al., 2014; Licht et al., 2008; Licht, de Geus, van Dyck, & Penninx, 2010). Only a handful of investigations have examined pretreatment HRV as a predictor of antidepressant outcomes in MDD. Early studies ($N \leq 25$) did not find any significant associations between baseline autonomic characteristics and antidepressant outcomes (Agelink et al., 2001; Agelink, Ullrich, Baumann, Strum, & Majewski, 2002).

In integrating the clinical and autonomic literatures, HF-HRV appears to be particularly relevant to anxious depression. Autonomic theories, including the neurovisceral integration model, describe tonic reduction in HF-HRV and posit significant relations with anxiety (Friedman, 2007; Porges, 1995; Thayer & Lane, 2009; Thayer et al., 2012). In support of these formulations, various anxiety disorders have been associated with reduced HRV (e.g., Chalmers, Quintana, Abbott, & Kemp, 2014; Licht, de Geus, van Dyck, & Penninx, 2009). Moreover, some investigators have found that low HF-HRV in MDD is driven or exacerbated by co-occurring anxiety (Chang et al., 2013; Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012; Watkins, Grossman, Krishnan, & Blumenthal, 1999).

In the current study, we investigated the predictive utility of pretreatment HF-HRV in anxious versus nonanxious depression, utilizing data from the iSPOT-D. Our hypotheses were based on the formulation that if higher resting HF-HRV reflects more adaptive functioning (Porges, 1995; Thayer et al., 2012), higher HF-HRV at baseline may index a more adaptive, flexible, or responsive physiological system that is able to benefit more strongly from antidepressant treatment. Further, given evidence that anxiety may drive or exacerbate associations between MDD and HF-HRV, these effects of HF-HRV on treatment response may be strongest for anxious depression. Therefore, we hypothesized that higher resting levels of HF-HRV would predict higher rates of response and remission across medication conditions, and that these effects would be significantly stronger for patients with anxious depression than for patients with nonanxious depression (i.e., that there would be a significant interaction between anxious depression and HF-HRV). In addition, given that MDD and treatment also have been associated with HR (Olbrich et al., 2016), we explored the parallel effects of pretreatment HR. Consistent with the predictions for HF-HRV, we hypothesized that lower resting HR, considered to be more adaptive, would predict higher rates of response and remission across conditions, and further, that these effects would be significantly stronger for anxious than for nonanxious depression.

## 2 | MATERIALS AND METHODS

### 2.1 | Overview of design and participants

iSPOT-D is a large, randomized, multicenter practical trial designed to identify predictors and moderators of antidepressant outcomes in MDD. Complete information on the trial design, protocol, and procedures is reported in Williams et al. (2011), and acute phase outcomes are reported in Saveanu et al. (2015). Participants were 1,008 adult men and women, ages 18–65 years, with first-onset or recurrent nonpsychotic MDD (56.6% female; age: $M = 37.84$ years). Patients were recruited through community settings at 17 international sites (see Supporting Information 1 for CONSORT diagram). A primary diagnosis of MDD was established using the Mini-International Neuropsychiatric Interview (MINI-Plus; Sheehan et al., 1998) following DSM-IV criteria and $HRSD_{17}$ total score $\geq 16$ (Hamilton, 1960). The MINI-Plus is a brief, structured diagnostic interview assessing common mental disorders with strong diagnostic reliability and convergent validity (Sheehan et al., 1998). Patients were antidepressant naïve, not on antidepressants currently, or were on antidepressants and completed a wash-out of at least five half-lives of any previously-prescribed antidepressants (see Supporting Information 2 for inclusion/exclusion criteria). The study was approved by all local institutional review boards. Patients provided written informed consent. The current analyses of HRV and hypothesized interactions with anxious depression were proposed a priori to the iSPOT-D publication committee.

### 2.2 | Pretreatment assessments

Patients completed the pretreatment assessments at week 0.

### 2.3 | Anxious and nonanxious depression

The $HRSD_{17}$ was completed by blinded licensed MD or PhD clinicians. The $HRSD_{17}$ is a 17-item clinician-administered instrument

that measures the severity of MDD symptoms with good reliability (Trajković et al., 2011) and validity (Hamilton, 1960). Categorical anxious depression was defined as $HRSD_{17}$ anxiety/somatization subscale score ≥ 7, and nonanxious depression was defined as $HRSD_{17}$ anxiety/somatization subscale score < 7 (Saveanu et al., 2015). These definitions were based on established cutoffs (Cleary & Guy, 1977) and were the same as those used in STAR*D (Fava et al., 2008) and other treatment studies (Domschke et al., 2010; Papakostas & Larsen, 2011). The distribution of $HRSD_{17}$ anxiety/somatization subscale scores in this sample (Supporting Information 3) was similar to that in STAR*D (Fava et al., 2008).

## 2.4 | Resting HRV functioning

Patients completed two 2-min seated recording periods, first with eyes open and second with eyes closed. Activity was recorded continuously at a sampling rate of 500 Hz, with 22-bit resolution digitization, using the NuAmps system (Compumedics Neuroscan, NC, USA) and standard prespecified software (Gatt et al., 2010). Electrocardiogram (ECG) electrodes were positioned on the inner left wrist at the radial pulse and on the right clavicle. The ECG tachogram data were generated using a modified Tompkins algorithm (Pan & Tompkins, 1985) and rectified using a semi-automated method, in which the cardiac R-wave thresholds for checking, cleaning, deleting, and marking for manual checking were previously established as optimal in the BRAINnet Database normative sample of 3,563 recordings (Koslow, Wang, Palmer, Gordon, & Williams, 2013). Time domain HRV was extracted as the root mean square of the differences between consecutive RR intervals (RMSSD). RMSSD values were normalized using natural log transformation. HR was extracted from the RR intervals as the average beats per minute. RMSSD and HR each were averaged across the eyes-open and eyes-closed periods, both to increase reliability and because of the high correlations between values for the two periods (RMSSD: $r = 0.94$; HR: $r = 0.97$), and centered for analysis. We selected RMSSD a priori as a common (Kemp et al., 2010; Rottenberg, 2007) and cost-effective (Goedhart, van der Sluis, Houtveen, Willemsen, & de Geus, 2007) metric of HF-HRV. RMSSD is also highly correlated with other measures of respiratory sinus arrhythmia including HF power, both in the general literature ($r = 0.85$) (Berntson et al., 1997; Goedhart et al., 2007) and current study ($r = 0.96$). RMSSD and HR data were missing for 41 patients, and 21 patients had data for only one period that was used as the average, primarily due to technical issues. Higher baseline MDD symptom severity ($HRSD_{17}$) was marginally associated with lower RMSSD ($r = -0.07$, $P = 0.076$), and was not significantly associated with HR ($r = 0.03$, $P = 0.467$).

## 2.5 | Demographic, clinical, and medical variables

Demographic information was obtained by study personnel via patient self-report forms. Current severity of MDD symptoms was assessed with the $HRSD_{17}$ and Quick Inventory of Depressive Symptomatology (Self-Report) ($QIDS\text{-}SR_{16}$; Rush et al., 2003). The $QIDS\text{-}SR_{16}$ is a 16-item self-report measure assessing the severity of depressive symptoms, and it has good reliability and convergent validity with clinician-administered instruments (Rush et al., 2003; Trivedi et al., 2004). Patients also self-reported on the presence of comorbid medical conditions across 17 body systems; finally, body mass index (BMI) was recorded.

## 2.6 | Protocol treatment

Patients were randomized (1:1:1) to receive escitalopram, sertraline, or venlafaxine-XR. Patients' usual treating clinicians adjusted doses based on their routine practices. Consistent with the practical trial design, patients and treating clinicians were not blind to treatment assignment. Prior to baseline assessments and initiation of protocol treatment, patients discontinued all psychotropic medications for at least 1 week, with the exception of sleep aids and anxiolytics that were discontinued within 24 hr of assessments.

## 2.7 | Outcome measures

At week 8, current severity of MDD symptoms was reassessed using the $HRSD_{17}$ and $QIDS\text{-}SR_{16}$. Consistent with the acute phase outcomes analyses (Saveanu et al., 2015), we utilized as primary outcomes clinician-reported rates of response and remission on the $HRSD_{17}$, defined as ≥50% reduction in total score from weeks 0 to 8 and total score ≤ 7 at week 8, respectively. Interrater reliability was audited using video methods, and internal consistency across raters was good (ICC = 0.87). We utilized as secondary outcomes self-reported rates of response and remission on the $QIDS\text{-}SR_{16}$, defined as ≥50% reduction in total score from weeks 0 to 8 and total score ≤ 5 at week 8, respectively. Side effects were assessed at week 8 using the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER), a three-item self-report instrument that has strong reliability and construct validity (Wisniewski, Rush, Balasubramani, Trivedi, & Nierenberg, 2006). At weeks 2, 4, and 6 by phone, and at week 8 in person, study personnel monitored medication dosage, compliance, concomitant medications, and adverse events.

## 2.8 | Statistical analyses

For the main analyses, we used logistic regression in Stata/SE 13.0 (StataCorp) to examine RMSSD and HR as predictors of treatment outcomes (response and remission on the $HRSD_{17}$ and $QIDS\text{-}SR_{16}$, assessed categorically; dummy-coded: 0 = lack of response/remission, 1 = response/remission). We tested anxious versus nonanxious depression (dummy-coded: 0 = nonanxious depression, 1 = anxious depression) as a moderator of the RMSSD and HR effects. Because we did not predict that RMSSD would moderate response to type of antidepressant, we included main effects of treatment condition (dummy-coded 0/1 for each condition) as covariates. Finally, we included several control variables. Some investigators have suggested that reduced HRV in MDD is attributable, in part, to comorbid cardiovascular and/or to respiratory medical conditions (Kemp et al., 2010; Kierlin & Yan-Go, 2009); therefore, we controlled for the presence of comorbid conditions in these two systems (dummy-coded 0/1 for each system). In addition, we controlled for race/ethnicity (categorical with five levels) and BMI, given their relation to HRV in other studies (Hill et al., 2015; Koenig et al., 2014). Consistent with previous

analyses in iSPOT-D, we also controlled for age, gender (dummy-coded: 0 = female, 1 = male), education, study site (categorical with seven levels), and baseline MDD symptom severity ($HRSD_{17}$). All variance inflation factor values were ≤ 3.6 and tolerance values were ≥ 0.28.

## 3 | RESULTS

### 3.1 | Participant characteristics by anxious versus nonanxious depression

Seven hundred and twenty-two patients completed the week 8 assessment. As shown in Table 1, 309 patients (42.80%) were defined as having anxious depression. Relative to the group with nonanxious depression, the group with anxious depression was significantly younger ($t$[633.89] = 2.19, $P$ = 0.029), had a lower proportion of Black participants and higher proportion of Asian participants (overall $\chi^2$[4,$N$ = 718] = 16.66, $P$ = 0.002), more severe depressive symptoms ($HRSD_{17}$: $t$[531.72] = −13.38, $P$ < 0.001; QIDS-$SR_{16}$: $t$[691] = −3.90, $P$ < 0.001), higher rates of comorbid cardiovascular ($\chi^2$[1,$N$ = 719] = 5.75, $P$ = 0.017) and respiratory ($\chi^2$[1,$N$ = 721] = 6.89, $P$ = 0.009) conditions, and a lower BMI ($t$[686] = 2.94, $P$ = 0.003). The two groups did not differ significantly with respect to gender composition ($\chi^2$[1,$N$ = 722] = 1.26, $P$ = 0.261), education ($t$[720] = −0.57, $P$ = 0.569), rates of treatment assignment (overall $\chi^2$[2,$N$ = 722] = 0.06, $P$ = 0.969), or medication dosages at week 8 (escitalopram: $t$[231] = −0.35, $P$ = 0.724; sertraline: $t$[243] = 0.57, $P$ = 0.572; venlafaxine-XR: $t$[229] = 0.10, $P$ = 0.921). Interestingly, the groups also did not differ significantly in RMSSD ($t$[679] = 0.40, $P$ = 0.690) or HR ($t$[679] = −0.60, $P$ = 0.546).

### 3.2 | Autonomic predictors of outcomes by anxious versus nonanxious depression

Table 2 presents the complete results for RMSSD and HR, anxious (versus nonanxious) depression, and their interactions as predictors of the primary and secondary outcomes. There were no significant main effects for RMSSD, HR, or anxious depression on any outcomes. As hypothesized, however, anxious depression significantly moderated the effects of RMSSD in predicting response rate on the $HRSD_{17}$ (interaction term: odds ratio [OR] = 2.16, 95% confidence interval [CI] = 1.15–4.02, $P$ = 0.016) and QIDS-$SR_{16}$ (interaction: OR = 2.12, 95% CI = 1.13–4.00, $P$ = 0.020), and remission rate on the QIDS-$SR_{16}$ (interaction: OR = 1.96, 95% CI = 1.04–3.70, $P$ = 0.038). In addition, anxious depression was a marginally significant moderator of the effect of RMSSD in predicting remission rate on the $HRSD_{17}$ (interaction: OR = 1.79, 95% CI = 0.96–3.34, $P$ = 0.068).

Figure 1 displays these moderating effects. In the group with anxious depression, patients with higher pretreatment RMSSD had higher response and remission rates, whereas patients with lower pretreatment RMSSD had lower response and remission rates. In the group with nonanxious depression, patients with lower RMSSD had better outcomes, whereas patients with higher RMSSD had poorer outcomes. Tests of the simple slopes indicated that in the group with anxious depression, RMSSD was significantly positively associated with response rate on the QIDS-$SR_{16}$ ($P$ = 0.007) and remission rate

**TABLE 1** Participant pretreatment characteristics as a function of anxious depression versus nonanxious depression

| Patient groups | Anxious depression ($N$ = 309) $M$ ($SD$) or $N$ (%) | Nonanxious depression ($N$ = 413) $M$ ($SD$) or $N$ (%) | $P$-value |
|---|---|---|---|
| Demographic characteristics | | | |
| Age (years) | 37.37 (13.14) | 39.47 (12.15) | 0.029 |
| Gender (female) | 185 (59.87%) | 230 (55.69%) | 0.261 |
| Race/ethnicity[a] | | | 0.002 |
| Non-Hispanic White | 189 (61.17%) | 259 (62.71%) | |
| Black | 42 (13.59%) | 79 (19.13%) | |
| Hispanic/Latino | 18 (5.83%) | 34 (8.23%) | |
| Asian | 31 (10.03%) | 18 (4.36%) | |
| Other | 27 (8.74%) | 21 (5.08%) | |
| Education (years) | 14.68 (2.92) | 14.56 (2.81) | 0.569 |
| Clinical characteristics | | | |
| $HRSD_{17}$ | 24.01 (4.29) | 20.17 (3.08) | <0.001 |
| QIDS-$SR_{16}$[b] | 15.16 (3.79) | 14.01 (3.87) | <0.001 |
| Comorbid cardiovascular condition[c] | 45 (14.56%) | 37 (8.96%) | 0.017 |
| Comorbid respiratory condition[d] | 60 (19.48%) | 51 (12.35%) | 0.009 |
| BMI[e] | 26.75 (6.68) | 28.37 (7.49) | 0.003 |
| Autonomic characteristics[f] | | | |
| RMSSD (log) | 3.32 (0.70) | 3.35 (0.67) | 0.690 |
| HR | 71.12 (10.80) | 70.62 (10.56) | 0.546 |
| Treatment assignment | | | |
| Escitalopram | 100 (32.36%) | 136 (32.93%) | 0.872 |
| Sertraline | 109 (35.28%) | 142 (34.38%) | 0.803 |
| Venlafaxine-XR | 100 (32.36%) | 135 (32.69%) | 0.926 |
| Dosage at week 8 (mg/day)[g] | | | |
| Escitalopram | 12.78 (9.12) | 12.33 (9.78) | 0.724 |
| Sertraline | 58.87 (31.43) | 61.28 (34.37) | 0.572 |
| Venlafaxine-XR | 76.31 (42.47) | 76.87 (41.33) | 0.921 |

BMI, body mass index; HR, heart rate; $HRSD_{17}$, Hamilton Rating Scale for Depression; QIDS-$SR_{16}$, Quick Inventory of Depressive Symptomatology (Self-Report); RMSSD, root mean square of differences of successive RR intervals.

[a]Data were missing for four patients; therefore, proportions do not sum to 100%.

[b]Data were missing for 29 patients.

[c]A total of 82 participants had a comorbid cardiovascular condition. Data were missing for three patients.

[d]A total of 111 participants had a comorbid respiratory condition. Data were missing for one patient.

[e]Data were missing for 34 patients.

[f]Data were missing for 41 patients. When also controlling for $HRSD_{17}$, the groups with anxious versus nonanxious depression did not differ significantly in RMSSD ($F$[1,678] = 0.22, $P$ = 0.638) or HR ($F$[1,678] = 0.09, $P$ = 0.762).

[g]Data were missing for 10 patients.

**TABLE 2** HF-HRV and HR predictors of treatment outcomes as a function of anxious depression versus nonanxious depression

| | $HRSD_{17}$ response | | $HRSD_{17}$ remission | | QIDS-$SR_{16}$ response | | QIDS-$SR_{16}$ remission | |
|---|---|---|---|---|---|---|---|---|
| **Outcome measures[a]** | **OR** | ***P*-value** | **OR** | ***P*-value** | **OR** | ***P*-value** | **OR** | ***P*-value** |
| Primary predictors | | | | | | | | |
| RMSSD (log) | 0.68 | 0.118 | 0.70 | 0.144 | 1.00 | 0.991 | 0.93 | 0.756 |
| HR | 0.98 | 0.173 | 0.98 | 0.188 | 1.02 | 0.242 | 1.02 | 0.223 |
| Anxious depression[b] | 1.22 | 0.352 | 1.23 | 0.326 | 1.13 | 0.555 | 1.01 | 0.968 |
| RMSSD (log) × Anxious depression | 2.16 | 0.016 | 1.79 | 0.068 | 2.12 | 0.020 | 1.96 | 0.038 |
| HR × Anxious depression | 1.05 | 0.024 | 1.05 | 0.013 | 1.03 | 0.184 | 1.01 | 0.512 |
| Baseline covariates | | | | | | | | |
| Age (years) | 0.98 | 0.018 | 0.98 | 0.056 | 0.99 | 0.245 | 0.99 | 0.550 |
| Gender [c] | 0.97 | 0.861 | 0.89 | 0.520 | 1.15 | 0.434 | 1.11 | 0.562 |
| Ethnicity [d] | 0.69–1.33 | ≥0.169 | 0.89–1.76 | ≥0.126 | 0.77–1.07 | ≥0.452 | 1.09–1.38 | ≥0.360 |
| Education (years) | 0.99 | 0.692 | 0.99 | 0.843 | 1.06 | 0.077 | 1.05 | 0.120 |
| Baseline $HRSD_{17}$ | 0.99 | 0.595 | 0.92 | 0.005 | 1.07 | 0.011 | 0.97 | 0.272 |
| Comorbid cardiovascular condition[e] | 1.30 | 0.374 | 0.95 | 0.848 | 0.81 | 0.469 | 1.09 | 0.792 |
| Comorbid respiratory condition[e] | 0.80 | 0.366 | 0.92 | 0.732 | 0.73 | 0.208 | 0.54 | 0.019 |
| BMI (log) | 2.39 | 0.364 | 4.82 | 0.095 | 1.02 | 0.986 | 0.47 | 0.414 |

BMI, body mass index; HR, heart rate; $HRSD_{17}$, Hamilton Rating Scale for Depression; HF-HRV, high-frequency heart rate variability; OR, odds ratio; QIDS-$SR_{16}$, Quick Inventory of Depressive Symptomatology (Self-Report); RMSSD, root mean square of differences of successive RR intervals.
Note: All models also included main effects of treatment condition and study site.
[a]Dummy-coded: 0 = lack of response/remission, 1 = response/remission.
[b]Dummy-coded: 0 = nonanxious depression, 1 = anxious depression.
[c]Dummy-coded: 0 = female, 1 = male.
[d]Categorical with five levels. OR and *p*-values represent ranges of values across the five levels.
[e]Dummy-coded: 0 = absent, 1 = present.

on the QIDS-$SR_{16}$ ($P = 0.033$). No other simple slopes from the models with interactive effects were significant (see Supporting Information 4 for standardized ORs as measures of effect size).

Also as presented in Table 2, anxious depression significantly moderated the effects of HR in predicting response rate on the $HRSD_{17}$ (interaction: OR = 1.05, 95% CI = 1.01–1.09, $P = 0.024$) and remission rate on the $HRSD_{17}$ (interaction: OR = 1.05, 95% CI = 1.01–1.09, $P = 0.013$). As shown in Figure 2, in the group with anxious depression, patients with higher pretreatment HR had higher response and remission rates on the $HRSD_{17}$, whereas patients with lower pretreatment HR had lower response and remission rates. The effects of pretreatment HR were opposing in the group with nonanxious depression. Tests of the simple slopes indicated that in the group with anxious depression, HR was significantly positively associated with remission rate on the $HRSD_{17}$ ($P = 0.049$) and response rate on the QIDS-$SR_{16}$ ($P = 0.008$). No other simple slopes from the models with interactive effects were significant (Supporting Information 4).

Three-way interactions among RMSSD, HR, and anxious depression were nonsignificant.

## 3.3 | Supplementary analyses

### 3.3.1 | Differences by treatment condition

We tested the possibility of three-way interactions among RMSSD or HR, anxious depression, and treatment type. There were no significant interactions (Supporting Information 5).

## 3.4 | Contribution of side effects

Given reports of greater antidepressant side effects in anxious depression (Fava et al., 2008), we examined RMSSD and HR, anxious depression, and their interactions as predictors of FIBSER scores. There were no significant main or interactive effects (Supporting Information 6). We also included FIBSER scores as additional control variables in the main analyses; all of the significant results either remained or were at even stronger levels of significance (Supporting Information 7).

## 3.5 | Contribution of anxiety disorder diagnoses

To examine the potential contribution of comorbid anxiety disorder diagnoses, we added to the primary analyses the main effect of any comorbid anxiety disorder (present vs. absent) and its interactions with RMSSD and HR. All of the previously-significant moderating effects of $HRSD_{17}$-defined anxious depression on RMSSD remained significant; however, the moderating effects of anxious depression on HR were not significant (Supporting Information 8).

## 3.6 | Contribution of other depression subtypes

Finally, given the documented overlap of the anxious depression subtype with both melancholic and atypical depression (Arnow et al., 2015), we added to the primary analyses the main effects of these other two subtypes and their respective interactions with RMSSD

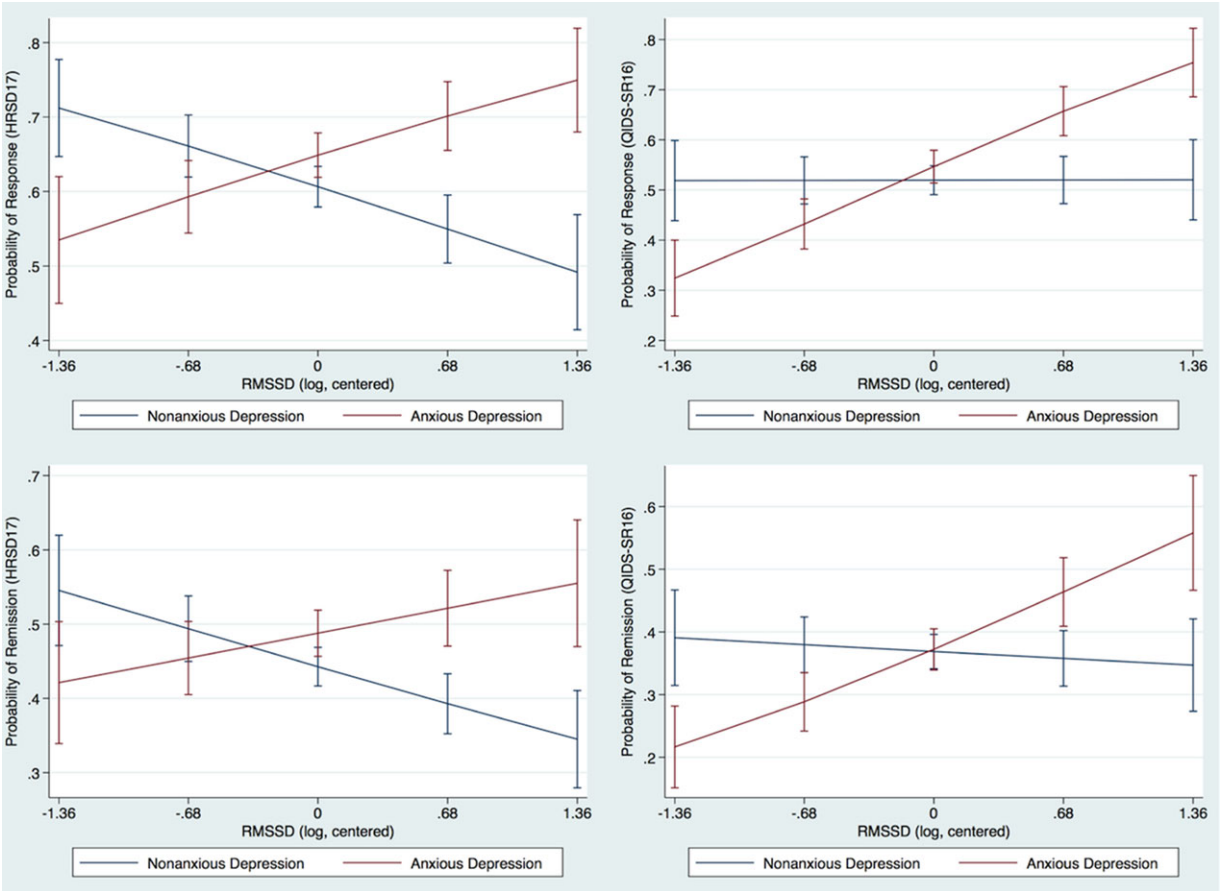


**FIGURE 1** Plots of the predicted probabilities of response/remission as a function of pretreatment high-frequency heart rate variability (root mean square of differences of successive RR intervals [RMSSD]) and anxious versus nonanxious depression. Clinician-reported response and remission on the Hamilton Rating Scale for Depression ($HRSD_{17}$) defined as ≥50% reduction in total score from weeks 0 to 8 and total score ≤ 7 at week 8, respectively. Self-reported response and remission on the Quick Inventory of Depressive Symptomatology (Self Report) ($QIDS\text{-}SR_{16}$) defined as ≥50% reduction in total score from weeks 0 to 8 and total score ≤ 5 at week 8, respectively. Results are adjusted for all other covariates in the models. Range of RMSSD represents mean ± 2 standard deviations. Values below −0.68 and above 0.68 each represent approximately 16% of patients. Error bars denote ± standard error

and HR. All of the previously-significant moderating effects of anxious depression on RMSSD and HR remained significant (Supporting Information 9).

## 4 | DISCUSSION

Pretreatment HF-HRV predicted antidepressant outcomes in MDD, but its specific effects were significantly different for patients with anxious versus nonanxious depression. As hypothesized, for patients with anxious depression, higher HF-HRV predicted better outcomes, whereas lower HF-HRV predicted poorer outcomes. However, for patients with nonanxious depression, the effects of HF-HRV were less consistent and no simple effects in this group were significant. Importantly, these results were obtained when controlling for several potential confounds (Kemp et al., 2010; Kierlin & Yan-Go, 2009; Nelson, 2008), including the severity of depression and comorbid cardiovascular and respiratory conditions. The current findings also were not attributable to patient demographic factors, BMI, antidepressant side effects, or other depression subtypes. Further, patients with anxious versus nonanxious depression did not differ in level of HF-HRV at baseline. Similar nonsignificant effects were reported in a prior large-scale study that included medicated participants (Kemp et al., 2014). Finally, the findings did not differ significantly by treatment arm, and the anxious and nonanxious depression groups did not differ in medication dosage. Thus, the effects of HF-HRV in anxious depression appear broadly applicable to three common antidepressant medications.

iSPOT-D was designed as a practical biomarker trial to identify predictors and moderators of antidepressant outcomes in MDD in a treatment-as-usual setting. The current results suggest that clinical (i.e., anxious depression) and biological (i.e., HF-HRV) assessments can be integrated to facilitate outcome prediction. Although anxious depression previously has been found to predict poorer response to antidepressants in some studies (Domschke et al., 2010; Fava et al., 2008; Papakostas & Larsen, 2011), this may operate only under conditions of relatively low HF-HRV. In fact, relatively high HF-HRV in anxious depression contributed to significantly better outcomes in this trial.

Higher resting HF-HRV has been found to be associated with multiple psychological processes, including more flexible, adaptive emotion

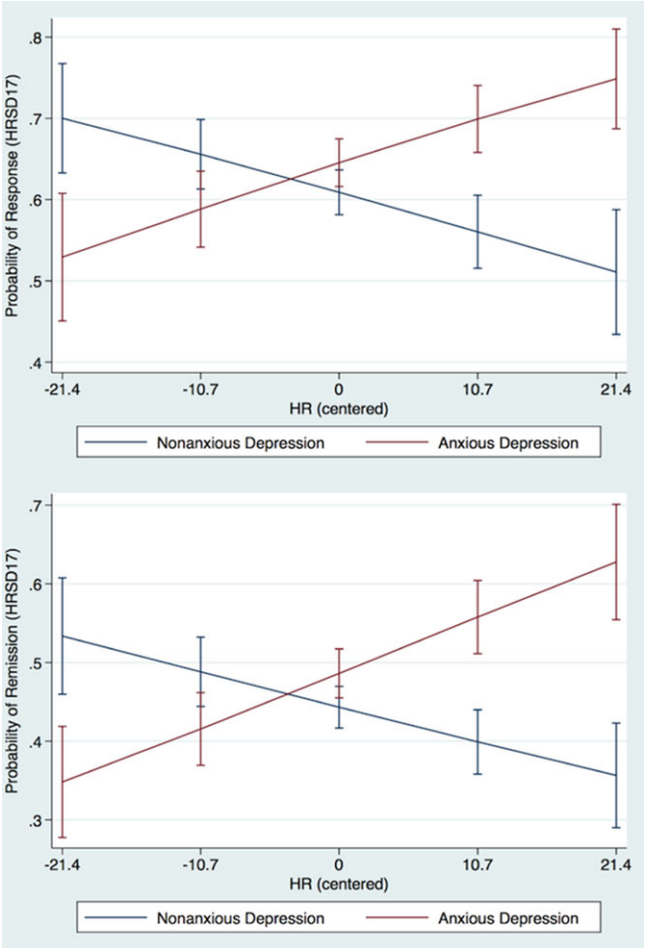


**FIGURE 2** Plots of the predicted probabilities of response/remission as a function of pretreatment heart rate (HR) and anxious versus nonanxious depression. Clinician-reported response and remission on the Hamilton Rating Scale for Depression ($HRSD_{17}$) defined as ≥50% reduction in total score from weeks 0 to 8 and total score ≤ 7 at week 8, respectively. Self-reported response and remission on the Quick Inventory of Depressive Symptomatology (Self Report) ($QIDS\text{-}SR_{16}$) defined as ≥50% reduction in total score from weeks 0 to 8 and total score ≤ 5 at week 8, respectively. Results are adjusted for all other covariates in the models. Range of HR represents mean ± 2 standard deviations. Values below −10.7 and above 10.7 each represent approximately 16% of patients. Error bars denote ± standard error

regulation and recovery in response to threat (Friedman, 2007; Thayer & Lane, 2009; Thayer et al., 2012). It is possible that higher HF-HRV in the context of higher anxiety, which is characterized by heightened threat sensitivity, indexes a more flexible or responsive physiological system that can benefit more strongly from antidepressant treatment. In contrast, HF-HRV in nonanxious depression may be indexing other, or more variable, psychobiological processes, which may explain its less consistent and diminished predictive capacity in these patients.

Both the clinical and HF-HRV assessments in iSPOT-D are feasible to conduct in many health care settings. In addition, the use of a threshold to operationalize anxious depression may be useful in clinical decision-making, which is typically categorical (e.g., to select a treatment based on whether or not a patient has anxious depression). Notably, however, we found significant effects only for $HRSD_{17}$-defined anxious depression, not for comorbid anxiety disorder diagnoses. Given the current results, it is possible that patients with anxious depression and relatively low HF-HRV would receive greater benefit from a different treatment approach. Future research could examine whether higher dosages, or alternative approaches, such as cognitive-behavioral therapy, may more effectively treat the sizeable population of patients with anxious depression and low HF-HRV. For example, cognitive-behavioral techniques that aim to increase flexibility in emotion regulation in response to threat or stress may help to target the clinical and cardiac profile of this group. It would also be interesting to explore models predicting outcomes over longer time periods (e.g., 12 weeks).

Several limitations of the present study warrant discussion. First, it is possible that these predictive effects differ in patients who are already taking medication; further research should examine this question. Second, based on the practical trial design of iSPOT-D, we included the sizeable proportion of participants with comorbid cardiovascular and respiratory conditions and controlled for these variables in the analyses. However, some studies of HF-HRV in MDD have excluded participants with such conditions (e.g., Kemp et al., 2010). While controlling for these variables addresses confounding statistically, it is possible that HF-HRV effects are distinct in samples without these comorbid conditions. Third, our total recording duration of 4 min was relatively short; future studies may utilize longer recording periods. Fourth, patients and treating clinicians were not blind to treatment assignment, and treating clinicians managed dose adjustments. These design choices were made to increase external validity in the translation to usual practice, but they decrease internal validity. Finally, this study did not include a control or placebo group, nor were HF-HRV and HR data collected at post-treatment. Future studies could integrate pre- and post-assessments for both active treatment and placebo groups in a fuller examination of mechanisms of treatment effectiveness. It is possible that changes in HF-HRV are associated with symptom improvement differentially in anxious versus nonanxious depression.

## 5 | CONCLUSION

HF-HRV, and in particular RMSSD (Goedhart et al., 2007), is a metric that could be used in current, routine health care practices. As such, it merits consideration in the context of the high costs to treat depression and the longer timeline to disseminate more complex brain-based and other biological assessments. Future research should focus on identifying more effective treatments for the subset of patients with both anxious depression and low HF-HRV, who exhibited reliably poor responses to antidepressant medication.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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