

Editorial

Heart Rate Variability before and after Antidepressant Treatment among Patients with Major Depressive Disorder: a Role for Adjunctive Sedative-Hypnotics?

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As specialists in cardiac autonomic dysregulation in depression, our research team members noted with interest, the paper in *Journal of Psychosomatic Research* in 2015 by Seldenrijk and co-workers, which reported that CVD incidence over 6 years of follow-up was particularly increased in depressed subjects with more severe symptoms and in those using benzodiazepines [1]. The result of the aforementioned research was the rationale behind our psychophysiological approach to discuss the possible underlying mechanism of these findings. Major Depressive Disorder (MDD) has a prevalence ranging between 8 and 12% worldwide, and will become the second biggest disease of burden by 2020, ranked just behind Cardiovascular Disease (CVD) [2]. Depressed patients have been shown to have an augmented risk of cardiovascular morbidity and mortality [3,4]. Specifically, Angst et al., [5] reported that MDD patients face a greater risk of cardiovascular mortality than general population, with the relative cardiovascular standardized mortality rates being 1.36 for MDD. Even though the definite mechanisms for this cardiac vulnerability are unknown, depression-associated reduction in Heart Rate Variability (HRV) is thought to be an important pathophysiological factor for this cardiac vulnerability [6,7]. Heart rate variability refers to the complex beat-to-beat variation in Heart Rate (HR) produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. A high degree of HRV aids healthy cardiac activity and provides a protective effect against myocardial infarction and heart failure, [8] whereas low HRV is an indicator of dysregulated cardiac autonomic

function and is associated with poor health [9] and an increased risk of CVD and mortality [6].

There has been an argument on the inconsistent findings regarding whether the observed reduction in HRV is inherent in depression [10,11] or due to the effect of antidepressants [12,13]. Research in this area has been hampered by the enrollment of patients with psychiatric and/or physical comorbidities that may confound HRV results. For example, MDD is frequently comorbid with anxiety disorders; approximately 20% of the patients with a lifetime diagnosis of MDD retrospectively report having had Generalized Anxiety Disorder (GAD) [14]. Previous research showed that GAD per se [15,16] were associated with decreased HRV.

A recent study indicated that unmedicated and physically healthy MDD patients with and without comorbid GAD had reduced HRV, and that those with comorbid GAD showed greater reductions in HRV [17]. Thus, a well-suited sample is needed to better examine the true effects of MDD on HRV. Our recent study showed that physically healthy, non-comorbid, and unmedicated patients with MDD had reduced HRV compared to healthy subjects, and that individuals with more severe depression are likely to have lower HRV than those with less severe depression [18]. These results point to a possible underlying mechanism behind the greater risk of cardiovascular mortality in MDD patients and provide further evidence that support the argument that the effect of reduced HRV is inherent in depression [11,17].

Most licensed antidepressants cannot restore the reduced HRV in depression, although they do effectively improve the depressive symptoms [11]. This phenomenon, on the one hand, reflects that an affective illness such as MDD might have residual effects on neurophysiological systems, as proposed previously [19,20]. On the other hand, it questions if any antidepressant can increase HRV in depressed patients and thereby conferring HRV mediated protective effects against increased risks for CVDs. Tricyclic Antidepressants (TCAs) are widely known to reduce parasympathetic tone and, thereby, HRV [11,21]. Evidence has pointed to the possibility of newer classes of antidepressants that act as serotonin and norepinephrine reuptake inhibitors to cause reduction in HRV [22-24], with effects less pronounced than those of TCAs. [25] Other evidence suggested that selective serotonin reuptake inhibitors may decrease HRV [23] but have a lower impact on HRV than TCAs [13]. The effects of agomelatine, a recently introduced antidepressant, on HRV in depressed patients are not well known yet. The pharmacology of agomelatine is unique among licensed antidepressant drugs, as it possesses both melatonergic MT₁/MT₂ agonistic and 5-HT_{2c} antagonistic properties but no ability to interfere with the neuronal reuptake of serotonin, norepinephrine, or dopamine [26,27]. Our recent study showed that agomelatine monotherapy increased cardiac vagal tone, suggesting that it has a favorable cardiovascular safety profile [28]. This may be due to agomelatine's unique mode of action: a synergy between melatonergic and 5-HT_{2c} receptors. As suggested by a recent review, activation of melatonergic receptors modulates the tone of the autonomic nervous system [29]. Specifically, acute treatment with melatonin increased cardiac vagal

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tone [30] and attenuated sympathetic tone [31], whereas, chronic treatment led to the inhibition of sympathetic activity [32] and the improvement of baroreflex function [33]. On the other hand, activation of serotonergic 5-HT_{2c} receptors in the Nucleus Tractus Solitarius neurons inhibits vagal outflow to the heart [34], and this inhibitory action can be prevented by a selective 5-HT_{2c} receptor antagonist [35]. Nonetheless, the promising result regarding the effect that agomelatine has on HRV warrants further future research in various clinical contexts.

Clinical guidelines recommend monotherapy antidepressants for the treatment of MDD [36,37]. In real-world clinical practice, however, sedative-hypnotics are often prescribed together with antidepressants to treat comorbid anxiety and insomnia symptoms, although these drugs have few or no antidepressive effects [38]. Clinicians should be cautious when adding sedative-hypnotics to agomelatine for the treatment of patients with depression, since there are suggestions that benzodiazepines may lose their efficacy with long-term administration and that their chronic use carries risks of dependence. In addition, there is a suggestion that sedative-hypnotics per se markedly influence HRV, possibly through a central γ -Aminobutyric Acid mechanism involved in cardiac vagal control of heart rate [39,40]. This effect has been understated in the literature about the effect of antidepressants on HRV, possibly because earlier cross-sectional studies found that depressed participants taking only benzodiazepines did not differ from controls with respect to HRV [12,23]. However, there is much evidence from human studies showing HRV reducing effects associated with commonly used sedative-hypnotics including alprazolam [41], zolpidem [42], lorazepam [43,44], midazolam [43,45,46] and clonazepam [47]. These finding raises the important question of whether the HRV reducing effect of benzodiazepines is a possible mechanism behind benzodiazepine use-associated additional CVD risk in depressed patients [1]. If this is the case, then whether adding sedative-hypnotics to agomelatine would erase the potential beneficial effect of agomelatine monotherapy on HRV is to be a case of concern. Further randomized, placebo-controlled studies are needed to answer these questions.

All in all, MDD is associated with reduced resting-state HRV. Agomelatine monotherapy may have a beneficial effect on HRV in depressed patients. In real-world clinical practice, however, clinicians should weigh the pros and cons when adding sedative-hypnotics along with agomelatine for the treatment of depressed patients considering that agomelatine's beneficial effects may be offset by the potential negative effects of adjunctive sedative-hypnotics on HRV.

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