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Changes in Autonomic Regulation in Moderate Depressive Disorders

O. S. Antipova, V. N. Krasnov, and O. S. Trofimova

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We present here results from studies of the characteristics of autonomic disorders in moderately severe anxious and anxious-melancholic endogenomorphic depression. A total of 36 patients with recurrent depressive disorders and ongoing depressive episode of moderate severity (ICD-10) took part in the study and showed a reduction in the total variability of the heart rhythm with retention of the balance of activity of the sympathetic, parasympathetic, and suprasegmental ergotropic components of the autonomic nervous system. The authors interpret this as evidence for loss of functional flexibility in autonomic regulation, which is apparent clinically as a reduction in tolerance to normal loads and extreme reactions to them. These changes became more severe with increases in age, duration of illness, and number of depressive episodes in the history. Changes in the body's regulatory systems (particularly the autonomic) in depression are quite stable and do not achieve complete normalization with treatment.

Keywords: depression, autonomic nervous system, hart rhythm variability, selective serotonin reuptake inhibitors.

Assessment of autonomic regulation is a traditional direction in studies of the pathogenesis and sanogenesis of endogenomorphic[1] depression [2, 3, 6, 10, 13, 17, 19–21, 23–26, 30, 38–41, 44, 50–52, 54]. Autonomic disorders are seen at all stages of development of the depressive phase: from prodrome and manifestation to stabilization and reduction [17, 20–21, 25, 26, 48]. A number of studies [15, 17, 23] have shown that the autonomic characteristics of depression and anxiety disorders are often similar and require special approaches for their differentiation with the aim of improving diagnosis and, which is particularly important, for selecting treatments.

Classical concepts [25, 26] of sympathetic tone as an unavoidable characteristic of the clinical picture of affective phases have now been subjected to considerable re-examination and revision. This is partly due to the fact that descriptive studies in this area have addressed severe endogenous melancholic depression [6, 20, 21, 25, 26]. Moderate and mild depression with endogenomorphic features has received significantly less study. In addition, there have been significant changes in the methodology of studies of the autonomic system [8, 9, 22, 47], which has led to the development of new theoretical concepts of the functioning of the autonomic nervous system (ANS).

Signs of psychoautonomic syndrome in endogenomorphic depression are variable and depend on a number of factors, from the features of the clinical structure of depression and the constitutional-typological characteristics of the patient to the autonomotropic effects of the treatments used and the presence of comorbid somatic pathology. At the same time, despite the whole range of factors affecting autonomic regulation, the dynamics of functional activity and ANS reactivity in endogenomorphic depression are defined primarily by systemic clinical-pathogenetic patterns of changes in the physiological reactivity typical of these patients [6, 16, 17]. The stereotype of the dynamics of depression persists in different variants of the phasic course

Moscow Research Institute of Psychiatry, Russian Ministry of Health, Moscow, Russia; e-mail: olga-ant@rambler.ru.

[1]The term endogenomorphic depression refers to depression which, according to phenomenological and dynamic criteria, corresponds to the traditional understanding of endogenous unipolar or circular depression [17].

of illness relatively independently of the clinical structure of depression and the type of treatment [17]. Thus, selection of methods for autonomic studies acquires fundamental importance. From the point of view of physiological reactivity and the state of the body's regulatory systems, there is interest in testing methods based on analysis of heart rate variability (HRV) [2, 3, 31, 34–41, 46, 49, 52, 54]. Apart from measurements of the functional activity of the segmental and suprasegmental sections of the ANS, this method provides for evaluation of functional tension of autonomic regulation the adaptive potential of the body [1, 4, 5, 14, 19, 31–33, 42].

These points can be supplemented with the observation that the principles of selecting pharmacotherapy and defining therapeutic prognoses in endogenomorphic depression, taking account of the state of autonomic regulation, have received insufficient development. Further information on the dynamic characteristics of autonomic regulation in the clinical picture of depression and the autonomic effects of antidepressants of different groups is needed. Some clinical randomized studies have demonstrated that that selective serotonin reuptake inhibitors (SSRI) do not have any direct influences on measures of HRV [3, 35, 46], in contrast to antidepressants of other groups [46, 54].

We have suggested that the dynamics of measures of autonomic regulation (including HRV) on the background of treatment with antidepressants of the SSRI group is largely due to the patho- and sanogenetic changes in autonomic regulation characteristic of depression per se. All these points defined the theoretical basis of the present study, its aim, and its tasks.

The aim of the present work was to undertake a complex dynamic evaluation of mental status and autonomic regulation in mild and moderate unipolar depression with the purpose of optimizing the diagnostic process and the tactics for treatment of patients with antidepressants of the selective serotonin reuptake inhibitors (SSRI) group.

Achievement of these aims required solution of the following tasks: 1) assessment of the functional activity and reactivity of the ANS in patients with mild and moderate unipolar depression (on a medication-free background) compared with healthy subjects; 2) investigation of the therapeutic dynamics of the structural-dynamic characteristics of autonomic regulation (including HRV data) in mild and moderate unipolar depression at the active SSRI treatment stage; 3) establishment of the relationship between the characteristics of autonomic regulation of patients and the structural-dynamic clinical-psychopathological characteristics of depression.

Materials and Methods

Studies were performed at the Department of Affective Spectrum Disorders, Moscow Research Institute of Psychiatry, from 2008 to 2013, in compliance with all standard requirements in relation to informing the patients. The study was open and comparative.

Inclusion criteria for patients were: age 18–65 years; ICD-10 diagnoses [27] of recurrent depressive disorder, ongoing mild or moderate depressive episode. *Exclusion criteria* were schizophrenia spectrum disorder; delusional disorders; disorders of psychological (mental) development; bipolar spectrum affective disorders; severe depressive episodes (including at the psychotic level); risk of suicide; addictive disorders; epilepsy and epileptiform syndrome; psychoorganic syndrome, dementia; somatic and neurological diseases in that stage of decompensation.

The starting cohort consisted of 51 patients, though several patients were lost to the study because of treatment side effects, lack of treatment response, and development of allergic reactions.

Thus, the study group consisted of 36 patients aged 18–61 (mean 36.5 ± 10.1) years. These included 27 women (75%) and nine men (25%). The ongoing depressive episode met the criteria for moderately severe depression (approaching severe in some cases) in 88.8% of cases; illness was mild in the remaining cases. The duration of the depressive episode from onset to seeking medical advice ranged from one month to 2.5 years. The depressive episode was protracted in eight cases and chronic in three. Signs of therapeutic resistance were seen in five cases (13.9%). In 22 cases (61.1%), the affective phase developed on a residual organic background; 25 cases showed comorbid somatic pathology in the compensation stage. Five cases showed extensive alcohol consumption without formation of clinically defined dependence, and 10 patients smoked.

The total duration of affective disorders ranged from six months to 24 years. In 27 patients (75%), the course of illness was qualified as recurrent depression. In nine cases (25%), first depressive episodes of endogenomorphic structure were ongoing at the moment of the study, while recurrent depressive disorder was established during further review observations. The number of depressive episodes experienced (including ongoing episodes) ranged from one to ten and averaged 2.71 ± 1.76. Before manifestation of illness and during intermissions, 75% of cases showed neurotic reactions and states dominated by psychoautonomic, asthenic, subclinical hypothymic, anxious-phobic, and, more rarely, hypochondriac symptomatology.

The control group consisted of 32 essentially healthy subjects (23 women and nine men, mean age 34.75 ± 8.65 years). The study and control groups were comparable in terms of gender and age characteristics.

Clinical and psychopathological studies were performed as semi-structured clinical interviews using special cards [17]. The severity of anxiety and depression, treatment responses, and treatment efficacy were evaluated using psychometric studies using the Hamilton anxiety scale (HAM-A) and the Hamilton depression scale (17-point HAM-D).

Autonomic studies, apart from the methods described, were based on analysis of HRV, which was performed using a programmable VNS-Mikro system (Neirosoft, Ivanovo).

Autonomic status was assessed in the state of functional rest (in the lying position for 5 min), and autonomic reactivity and autonomic support for activity (on the background of an orthostatic test for 6 min) were evaluated. The time parameters of HRV were mean heart rate (HR, bpm), mean cardiointerval duration (RRNN, msec), mean square deviation (SDN, msec), coefficient of variation (CV, %), and the parameter RMSSD (msec). Total spectral power (TP, msec^2) characterized total HRV and was analogous to SDNN (msec) and CV (%) [1, 42].

RRNN and HR provide evidence relating to the level of functioning of the cardiovascular system during the time interval studied. SDNN reflects total HRV as an overall result of all regulatory factors influencing cardiac rhythm. SDNN increases with increases in total HRV and decreases with decreases. CV is a normalized assessment of total HRV and can be used to compare people with different HR. RMSSD is defined as the square root of the sum of the squares of the differences between sequential pairs of cardiointervals. RMSSD selectively reflects the activity of the parasympathetic ANS and is independent of sympathetic influences [1, 14, 19, 33, 42].

Spectral analysis of HRV is used to identify the reproducibility of the process of interest. HR variability results from the superimposition of regulatory processes of different types with different periods, amplitudes, and regularities. The essence of any method of spectral analysis is the detection of periodic components in oscillations of heart rate and assessment of their quantitative contributions to the total variability of the rhythm.[2]

The physiological mechanism of high-frequency oscillations (HF) consists of a sinusoidal respiratory arrhythmia: heartbeat accelerates with the onset of inspiration and slows during expiration. Spectral power in the HF range is almost completely determined by the activity of the parasympathetic nervous system [1, 14, 19, 32, 33, 42].

The physiological mechanisms of low-frequency oscillations (LF) are associated with sympathoadrenal baroreflex influences on the cardiac rhythm. Excitation of baroreceptors in the sinocarotid and aortic zones in response to increases in blood pressure lead to increases in afferent spike activity via the vagus and glossopharyngeal nerves, excitation of the cardioinhibitory center in the medulla oblongata, and suppression of cardiostimulatory and vasoconstrictor centers. This results in dilation of vessels, decreases in total peripheral vascular resistance, and decreases in HR. Decreases in BP lead to the reverse process [1, 14, 19, 32, 33,42]. The ratio of the functional activities of the sympathetic and parasympathetic components of the ANS is reflected by the LF/HF ratio [1, 42].

The origin of VLF oscillations has no general explanation. Non-Russian investigators have avoided physiological interpretation of this frequency range [42], while Russian authors have made attempts [1, 31]. In particular, Khasperkova [31] showed that the power of VLF oscillations is influenced by the activity of the cerebral ergotropic systems.

Our study consisted of two stages. The first stage involved analysis of autonomic regulation in patients on a medication-free background as compared with a control group. The second stage consisted of dynamic recording of a series of psychopathological, psychometric, and autonomic parameters in a group of patients. All parameters in the study group were assessed twice: before treatment initiation and at 4–6 weeks of treatment.

Autonomic measures were investigated in the control group on one occasion.

A total of 20 patients were treated with fluvoxamine (50–200 mg/day) and 16 with sertraline (50–200 mg/day). Vitamins B and C were prescribed on the basis of clinical indications; low doses of short-acting hypnotics (zolpidem, zopiclone) and non-benzodiazepine anxiolytics (etifoxine, afobasol, hydroxyzine) were given as indicated by symptomatology. Normothymics (carbamazepine, oxcarbazepine) were added after 4–6 weeks of treatment at the stage of establishing remission.

All patients were assessed prospectively for one year (autonomic assessments were not performed during this time). Review data were used to study the adaptation of patients and to identify the quality and stability of the remission achieved.

Study results were analyzed using the statistics computer program Statistica 6.0. Distributions were identified using the Kolmogorov–Smirnov test. Data with normal distributions were described in terms of the mean and standard deviation from the mean; data with non-normal distributions were described using the median and the 25–75% interquartile interval. In addition, statistical processing of the data used the Wilcoxon test for linked sets, for pairwise comparisons of values, the Mann–Whitney test for unpaired sets and nonparametric Spearman rank correlation analysis. Differences were regarded as significant at $p < 0.05$.

Results and Discussion

The structure of the depressive state in five patients (13.9%) was dominated by melancholic affect, while that in 12 patients (33.3%) was mainly melancholic-anxious; that in 13 patients (36.1%) was anxious, that in two (5.6%) was apathetic, and that in one (2.8%) was melancholic-apathetic. In three cases (8.3%), depression was defined as a hypothymic state with undifferentiated affect modality.

In many cases, the structure of the depressive state had primarily anxious-phobic, psychoautonomic, cenesthohypochondriac, and asthenic manifestations. Intrinsic depressive symptomatology, melancholic affect, and anxi-

[2] Using traces of duration 5 min, the HRV spectrum includes the following components: HF, i.e., high frequency, 0.15–0.4 Hz), LF (low frequency, 0.04–0.15 Hz), and VLF (very low frequency, 0.003–0.04 Hz). Power spectrum density in the HF, LF, and VLF ranges can be measured in absolute units (msec^2) or relative units (normalized, %) [1, 42].

ety were moderate. Anxiety was usually accompanied by phobias (mainly hypochondriac content), though it could reach the stage of "free floating" (87.5%). Apart from situational anxiety (75%) and hypothymic reactions (88.8%), autochthonous hypothymia was also seen.

Motivational-volitional disorders were characterized by marked decreases in the desire to act (generally compensated by volitional effort) and loss of interest in daily pursuits and events (75%). Anhedonia was seen in 88.8% of cases. Feelings of tiredness arose with daily workloads and transient physical and intellectual efforts (75%).

In the cognitive domain, there were decreases in the rate of performing simple mental operations (69.4%), impairments to concentration (100%) and switching of attention (22.2%), fatigue of attention, and decreases in the productivity of mental activity, and difficulty with decision-taking. Planning and targeting processes were degraded. These impairments were moderate in severity and partly controllable by volitional effort, though they hindered professional and social adaptation of the patients.

Low self-esteem (80.6%) was dominant or overvalued and was apparent as feelings of decreases in and loss of former intellectual, emotional, and physical qualities, as well as work productivity. Pessimistic assessments of self, immediate surroundings, and the future were characteristic. These feelings were could be temporarily corrected and retained conditional links with real circumstances. Ideas of self-incrimination (27.78%) were mainly seen in the melancholic, melancholic-anxious, and melancholic-apathetic variants of depression not reaching the delusional level. These were of the nature of a "moral sense of guilt." When the anxiety component of depressive affect was severe, there were hypochondriac ideas (25%), as well as differentiated ideas of condemnation in the form of "fears" of external assessments from those surrounding the patient (30.6%).

Motor disturbances in anxious depression were usually characterized by complex combinations of moderate retardation in the form of monotonousness and uniformity of movements, along with signs of arousal, restlessness, and animation of fine motor function (55.5%). Motor retardation with reduced expressivity of movement, slowing of movement speed, and loss of plasticity was more apparent in the melancholic and melancholic-apathetic variants (19.4%).

Disorders of vital drives were variable in structure. When the anxious affect was dominant, increases in appetite (11.1%) and libido (8.33%) could be seen, as could decreases (27.8% and 33.3%, respectively). As the severity of depression increased, the appearance of melancholic components in the structure of the state were more clearly apparent in terms of loss of appetite with loss of body weight (25%), reductions in libido, and taste and sexual anhedonia. Sleep disorders (88.8%) were generally apparent as a combination of early waking with marked impairments of going to sleep over 1.5–2 h. In addition, sleep disruption was characterized by distorted perception of sleep duration, though the complete "absence of the feeling of sleep" was not seen.

In the vast majority of cases (97.2%), circadian rhythms were seen in the emotional, affectogenic cognitive and conative disorders, with improvements in the evening hours.

Psychoautonomic disorders were an obligatory (and in many cases the leading) component of the clinical picture and their onset often anticipated hypothymic manifestations themselves. Patients presented complaints of pain and unpleasant sensations in the head (27.8%), abdomen (22.2%), chest (75%), and interscapular area (38.9%), as well as vertigo (22.2%), palpitations (75%), feelings of "fading" and "gaps" of the heartbeat (55.5%), poor inspiration and feelings of lack of air (88.8%), and lability of arterial blood pressure, mostly with a tendency to hypertension (69.4%). Dysuric disorders were seen less commonly, as were sweating, noninfectious subfebrile states, "hot flushes," and chills.

Sympathoadrenal or mixed anxious-autonomic attacks (single or repeated) were present in the structure of depression or during the prodromal period in 33.3% of cases. In seven, there were secondary noso- and/or agoraphobic symptoms and restricted behavior of different levels of severity.

Patients with anxious depression showed marked lability of autonomic responses with a tendency to amblytonia, i.e., the combination of sympathotonic and vagotonic manifestations, which is evidence of strong physiological reactivity and tendencies to excessive reactions to ordinary events. Somatic anxiety with fixation of autonomic manifestations dominated at the initial stages of development of depression. Increases in the severity of depression were linked with increases in feelings of melancholy, clearer vitalization of affect, and stable appearance of sympathotonia. There was a transformation of somatic anxiety to mental, with increases in its ideatory manifestations.

Patients' emotional responses to autonomic symptoms started to acquire a troublesome tone with the occurrence of life experiences. Patients produced different metaphors to describe the feelings they had experienced ("gurgling," "burning"), emphasizing the distinction from day-to-day experiences.

Psychometric study results were used to determine the severity of "anxiety" and "depression" on the corresponding scales. The total HAM-D points score before treatment initiation was 21.3 ± 9.8, and that on the HAM-A anxiety scale was 18.5 ± 6.2 (7.6 ± 3.7 and 8.1 ± 4.8 points on the mental and somatic anxiety subscales, respectively). This is evidence that anxious and depressive affect was of moderate severity.

Table 1 shows results obtained from HRV analysis in the control and study groups. Assessment of autonomic status in the patients group demonstrated lower total HRV than in the healthy group – SDNN was 37 (26.5–44) msec and 51.95 (38.45–61.1) msec, respectively ($p = 0.0002$); TP was 1414 (826–1935) msec^2 and 2609.5 (1488–3490) msec^2, respectively ($p = 0.0025$).

TABLE 1. Results of Investigations of the Autonomic Nervous System in Patients not on Medication and in Controls

Parameter	Study group (n = 36)		Control group (n = 32)	
	baseline trace	orthostatic test	baseline trace	orthostatic test
HR, bpm	71.5 [64.5–81]	86 [81–105]*	74.65 [66.45–78.1]	87.15 [83.6–96.05]*
RRNN, msec	839 [743–928]	697 [573–745]*	803.85 [768.2–905]	680.10 [624–715.65]**
SDNN, msec	37 [26.5–44]	37 [23–44]	51.95 [38.45–61.05]$^{\#}$	40.45 [32.9–55.6]*$^{\#}$
CV, %	4.45 [3.29–5.24]	4.8 [3.7–5.8]**	5.9 [4.6–7.7]$^{\#}$	6.43 [5.3–7.8]$^{\#}$
RMSSD, msec	32.5 [19–42]	15 [9–26]*	49.35 [24.3–66.3]$^{\#}$	20.00 [14.7–37.1]$^{\#}$
TP, msec^2	1414 [826–1935]	1101 [678–2006]	2609.5 [1488–3490.5]$^{\#}$	1981 [1034.5–3307.5]**$^{\#}$
VLF, %	33.86 [25.4–52.4]	53.3 [43.9–69.7]*	31.52 [21.14–46.89]	39.04 [27.2–49.8]$^{\#\#}$
LF, %	27.6 [17.4–36.1]	28.3 [16.5–38.7]	34.03 [29.86–43.44]$^{\#}$	41.21 [30.29–54.45]$^{\#}$
HF, %	28.6 [19.24–43.35]	10.9 [7.0–21.4]	27.6 [14.37–38.79]	12.31 [8.14–25.88]*
LF norm. n.u.	51.1 [31.4–62.4]	71.3 [54.3–81.3]*	59.6 [47.25–71.65]$^{\#}$	74.2 [57.6–86.8]**
HF norm. n.u.	48.9 [37.6–68.6]	28.7 [19.2–45.7]*	40.45 [28.35–52.75]$^{\#}$	25.8 [13.7–40.95]**
LF/HF	0.88 [0.46–1.66]	2.48 [1.19–4.34]*	1.48 [0.89–2.59]$^{\#}$	4.13 [1.53–6.96]*
KRS	6.6 [3.28–13.7]	4.86 [2.59–13]	4.92 [4.11–8.66]	3.87 [3.16–6.96]
K30/15		1.06 [1.03–1.07]		1.14 [1.02–1.22]

Notes. Here and Table 2: distributions of parameters were non-normal so descriptive statistics used the median and the 25–75% interquartile interval; statistically significant differences in paired sets (baseline – orthostatic test) in the study and control groups, Wilcoxon W test, *$p < 0.001$, **$p < 0.05$; statistically significant intergroup differences in non-paired sets (study and control groups), Mann–Whitney U test, $^{\#\#}p < 0.001$, $^{\#}p < 0.05$.

These data are consistent with results from a series of studies of autonomic regulation in different affective spectrum disorders [2, 31, 34, 37–41, 46, 49, 51, 52, 54]. In many studies, decreases in total HRV were simply presented, without any attempt at physiological interpretation.

Some investigators [3, 39] have suggested that total HRV is an indicator of functional flexibility (autonomic flexibility) in the autonomic regulatory system. From this point of view, decreases in total HRV constitute evidence of a decrease in the potential ability of the ANS to undergo adaptive rearrangements in response to various external stimuli.

Data obtained from studies of autonomic status did not identify any significant intergroup differences in relative spectral density in the VLF, LF, and HF ranges. In other words, the balance of activity in the suprasegmental ergotropic (VLF, %), sympathetic (LF, %), and parasympathetic (HF, %) components in the study cohort of patients remained as in the control group (see Table 1). This appeared to occur as a result of the fact that the physiological mechanisms of the "mutually stimulatory antagonism" [7, 45, 53], determining the sympathetic-parasympathetic balance, is relatively preserved in depression.

Overall, along with the reduction in total HRV, these data indicate that the whole system of autonomic regulation functions in a "disaster" regime, maintaining only the homeostatically important components (particularly the sympathetic-parasympathetic balance) of the "value" of the cost of regulatory flexibility, with shrinkage of adaptive potential. The consequence of this dysregulation is apparent as a reduction in the individual tolerance barrier for ordinary loadings, in many cases with extreme reactions to them [12].

It can be suggested that the final "fracture" in regulation, with formation of a new and stable pathological system, evidently occurs at later stages, as the severity increases and a "closed " structure of depression forms. In clinical terms, this corresponds to an increase in sympathetic tone and a decrease in autonomic reactivity as the depressive phase progresses.

To some extent, this suggestion is supported by correlation analysis results. Thus, negative correlations of intermediate strength were found between the total HAM-D points score and total HRV in the state of functional rest: SDNN ($r_s = –0.38$, $p = 0.028$), CV ($r_s = –0.40$, $p = 0.04$), and TP ($r_s = –0.36$, $p = 0.02$). In other words, the reduction in total HRV becomes greater as the severity of depression increases. These data are consistent with results reported by Stein et al. [52].

The results of comparative intergroup analysis of HRV obtained from studies of autonomic reactivity and the auto-

TABLE 2. Dynamics of HRV in Endogenous Depression at the Stage of Active Treatment with SSRI

Parameter	Baseline trace		Orthostatic test	
	before treatment initiation	4–6 weeks of treatment	before treatment initiation	4–6 weeks of treatment
HR, bpm	71.5 [64.5–81]	75.5 [66–80.5]	86 [81–105]*	94.5 [85.5–102]*
RRNN, msec	839 [743–928]	796.5 [745.5–908.5]	697 [573–745]*	633 [589–702]*
SDNN, msec	37 [26.5–44]	36 [27.5–52]	37 [23–44]	31.05 [22–39.5]**
CV, %	4.45 [3.29–5.24]	4.65 [3.4–6.38]	4.8 [3.7–5.8]**	4.47 [3.61–5.9]*
RMSSD, msec	32.5 [19–42]	30.5 [20.5–46.5]	15 [9–26]*	14 [8–22]
TP, msec^2	1414 [826–1935]	1328 [761–2304]	1101 [678–2006]	1080 [573–2071]
VLF, %	33.86 [25.4–52.4]	42.85 [32.3–56.7]##	53.3 [43.9–69.7]*##	51.75 [42.2–67.7]**
LF, %	27.6 [17.4–36.1]	20.75 [13.35–29.3]	28.3 [16.5–38.7]	28.23 [18.7–36.05]**
HF, %	28.6 [19.24–43.35]	30.04 [19.95–47.35]	10.9 [7.0–21.4]	10.41 [6.48–23.15]*
LF norm. n.u.	51.1 [31.4–62.4]	42.3 [31.75–61.5]	71.3 [54.3–81.3]*	66.65 [51.44–82]*
HF norm. n.u.	48.9 [37.6–68.6]	57.7 [38.5–68.3]	28.7 [19.2–45.7]*	33.35 [18–48.56]*
LF/HF	0.88 [0.46–1.66]	1.01 [0.47–1.6]	2.48 [1.19–4.34]*	2.01 [1.06–4.54]*
KRS	6.6 [3.28–13.7]	8.4 [3.38–16]	4.86 [2.59–13]	5.59 [3.19–10.93]
K30/15			1.06 [1.03–1.07]	1.06 [1.01–1.14]

Note. Comparison of HRV in baseline traces and orthostatic tests: statistically significant differences for paired sets, Wilcoxon W test, *$p < 0.001$, **$p < 0.05$; comparison of HRV before treatment and at 4–6 weeks of treatment: statistically significant intergroup differences for paired sets, Wilcoxon W test, ##$p < 0.05$.

nomic support for activity during the active orthostatic test are shown in Table 1. On the background of orthostasis, both the patients group and the healthy group showed decreases in the activity of vagal influences on heart rhythm (HF, %) (see Table 1). In the patients group, the decrease in parasympathetic reactivity in response to orthostatic loading increased with increases in the number of depressive episodes experienced ($r_s = –0.36$, $p = 0.032$) and the severity of anxiety on the HAM-A ($r_s = –0.41$, $p = 0.014$).

In contrast to healthy subjects, orthostatic loading in patients with depression was supported largely by increases in the activity of the suprasegmental ergotropic systems. This was reflected in the predominant increase in relative spectral power in the VLF range (see Table 1). In healthy subjects, orthostatic loading was supported by baroreflex mechanisms at the segmental level, as evidenced by the predominant growth in spectral power in the LF range (see Table 1).

According to correlation analysis data, the extent of activation of the suprasegmental ergotropic systems on orthostatic loading in patients with depression increased with age ($r_s = 0.52$, $p = 0.02$) and with increases in the duration of affective disorder ($r_s = 0.41$, $p = 0.013$). In addition, the older the patient, the more severe the suppression of reactivity of the sympathoadrenal baroreflex mechanisms ($r_s = –0.39$, $p = 0.019$). To some extent, these data are consistent with results reported by Jindal et al. [43] on assessments of HRV in elderly patients with depression.

A significant negative interaction was found between patients' age and the K30/15 coefficient, which directly characterizes the reactivity of the ANS in response to orthostatic loading ($r_s = –0.46$, $p = 0.018$). The K30/15 coefficient also correlated negatively with the number of depressive episodes experienced ($r_s = –0.59$, $p = 0.018$) and the total duration of the affective disorder ($r_s = –0.54$, $p = 0.006$). In other words, the older the patient, the longer-lasting the illness, and the larger the number of episodes experienced, the lower the reactivity of the ANS in supporting orthostasis.

These results are supported by some studies [39, 51] addressing patients with depressive disorder. Similar HRV dynamics on the background of orthostasis correspond to the phenomenon of a decrease in baroreflex sensitivity, which is explained by the inhibitory influences of extremely active suprasegmental ergotropic systems [11, 29, 39]. Like reductions in total HRV, this pathophysiological mechanism is universal for different pathological states whose pathogenesis involves distress [18, 28, 29].

The involvement of the central components of autonomic regulation in the process maintaining loads such as orthostasis, which is "simple" for the body, appears to con-

stitute evidence of a decrease in the adaptive potential and a reduction in the plasticity of physiological reactions in depression. This may be apparent as a loss of harmonicity and concordance in the functioning of different components of the ANS, especially when there is a need to adapt to external influences.

Dynamic evaluation of clinical-psychopathological and psychometric characteristics on the background of the active stage of treatment with SSRI demonstrated a clinically characteristic response to treatment in most patients (88.8%). Of the patients included in the study cohort, lack of response by 4–6 weeks was seen in only four cases.

The clinical dynamics were characterized by virtually complete reduction in autochthonous anxious and hypothymic manifestations, normalization of appetite, and improvement in sleep. There was a significant reduction in the severity of the cognitive and conative components of depression, though complete recovery did not occur at this stage. Daily affective oscillations in the patients' mood and activity were largely smoothed out. Some cases showed persistence of moderately severe anxious-melancholic symptomatology for 1–2 h after waking.

Most patients showed a significant decrease in the severity of depression, while eight patients showed formation of a clinically characteristic remission. The main feature was situational anxiety and hypothymic reactions, with some cases showing residual phobic and hypochondriac symptomatology and signs of asthenia.

Complete reductions in autonomic abnormalities generally did not occur, though their polymorphism, frequency, and severity decreased. Emotional saturation of autonomic disorder-linked experiences decreased significantly, and anxious-hypochondriac apprehension lost its subjective immediacy. Exacerbation of comorbid somatic pathology (manifestations of radiculopathy, onset or increase in the frequency of migraine attacks, BP lability) occurred in seven cases, along with increases in the clinical signs of autonomic lability at the stage of establishment of remission. The clinical dynamics showed significant reductions in psychometric measures. At 4–6 weeks of treatment, the total HAM-D score was 12.3 ± 6.8 ($p = 0.0005$) and the HAM-A anxiety score was 11.5 ± 5.1 ($p = 0.038$), 5.6 ± 2.7 ($p = 0.0035$), and 6.1 ± 3.8 ($p = 0.0027$) points on the mental and somatic anxiety subscales, respectively.

Results obtained from dynamic HRV analysis on the background of treatment with SSRI (fluvoxamine, sertraline) are shown in Table 2. Despite the clinically marked improvement (including in relation to somatoautonomic disorders), there were no statistically significant differences in HRV parameters at 4–6 weeks of treatment. This appears to support the view that systems changes in the functioning of the body's regulatory systems (particularly the autonomic) are quite stable in depression and complete recovery occurs much later or does not reach normative values at all. These data are to some extent based on the need for long-term treatment courses. In this regard, there is interest in comparing responder and nonresponder groups, though this requires further studies with larger cohorts and greater volumes of experimental data.

Studies of the relationships between measures of autonomic regulation on the background of treatment with factors characterizing the course of depression using formal assessments based on Spearman rank correlation identified a series of features. The results showed that the larger the number of depressive episodes experienced by the patient, the longer activation of suprasegmental ergotropic systems (VLF, %; $r_s = 0.4$, $p = 0.02$) and decreased parasympathetic tone (HF, %; $r_s = -0.4$, $p = 0.02$) persisted on the background of treatment.

In addition, at 4–6 weeks of treatment, orthostasis identified a negative correlation of intermediate strength between patients' age and the activity of sompathoadrenal baroreflex systems (LF, %; $r_s = -0.4$, $p = 0.02$). In other words, the older the patient, the slower the recovery of the baroreflex sense on the background of SSRI treatment.

In conclusion, studies of the characteristics of autonomic regulation in depressive states remain a problem in psychiatry. Further development is not only needed for providing theoretical grounds for the pathogenetic and sanogenetic mechanisms of endogenomorphous depression and identification of the clinical-pathogenetic pattern of its dynamics, but also has relevance to the search for criteria for individual prognostication and for employing a differential approach to selecting treatment tactics taking cognizance of data on autonomic functions. Further studies will be of value for developing approaches to the complex evaluation of responses to treatment with SSRI antidepressants with consideration of the dynamic characteristics of autonomic regulation.

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