AN IGNORED FACTOR IN DEPRESSION PATHOGENESIS: CHRONIC CO-MORBIDITY OF LOW BLOOD PRESSURE AND CERVICAL SPINE SYMPTOMS

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Игнорируемый фактор в патогенезе депрессии: коморбидность гипотензии и цервикального синдрома

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Today, depression is considered one of the most common diseases, second only to infectious diseases. According to the latest findings, most antidepressants have more side effects than real therapeutic effects. Obviously, the pathophysiological mechanisms of this disease have not yet been sufficiently understood in order to develop appropriate therapeutic approaches. In systematic studies in 425 patients with a resting systolic blood pressure of <110 mmHg we have been able to verify the triad of low blood pressure, cervical spine syndrome, and depressive disorders. Symptoms in these patients were partially or fully relieved after 2 to 4 weeks in which they followed a special Asclepian treatment without any medication aimed at a healthy life style.

Сегодня депрессию считают одной из наиболее распространенных болезней, уступающую только инфекционным заболеваниям. Согласно последним данным, у большинства антидепрессантов есть больше побочных эффектов чем реальных терапевтических. Очевидно, патофизиологическое механизмы этой болезни еще недостаточно поняты для развития адекватных терапевтических подходов. В систематических исследованиях на 425 пациентах с гипотензией (<110 mmHg) мы верифицировали триаду симптомов пониженного давления, цервикалгии и депрессии. Большинство симптомов частично или полностью устранялись после 2—4 недель применения лечения по методике Асклепия, нацеленного на здоровый образ жизни.

Introduction

With a lifetime prevalence of 10-18% and a point prevalence of 7%, depressive disorders are among the most common diseases in Germany [1,2]. At a crisis conference of the European Section of the WHO, held in Brussels in June, 1999, and dedicated to psychosocial health, the alarming development of mental disorders, in particular that of depression, was discussed. Worldwide, 350 million people are reported to be suffering from depression [3]. The successful treatment of depressive disorders is often considered difficult [3]. The therapeutic effectiveness of antidepressants is currently being criticized. In the Medical Drug Prescription Report (Arzneiverordnungsreport) 2009, edited by Schwabe and Pfaffrath, Lohse and Müller-Oerlinghausen provide the following assessment [4, p. 774: «There is no need to treat all cases of depression with drugs, because there are well validated non drug treatment options available» For mild depression, according to the latest guidelines, antidepressants are no longer considered the preferred agent in primary therapy [5]. Their efficacy is limited and also relatively unspecific.

These reports on the low efficacy of various antidepressants suggest that representatives of pharmaceutical science are pursuing a false therapeutic approach that is founded on and incomplete understanding of the pathophysiology of depression. Therefore, it is understandable that the search for new approaches in the treatment of those affected by depression has become an extreme necessity. Numerous authors see stress, in particular unresolved chronic emotional distress that has become uncontrollable, or post-traumatic stress disorder (PTSD) as «early stages» of depressive disorders. In the presence of unresolved emotional distress patients feel helpless and hopeless, which in turn presents as melancholia (depression). This is reflected by an excessive increase in stress hormones such as corticotropine releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol.

Research has shown that:

— Neuroplasticity is limited by the inhibition of cerebral neurogenesis as a consequence of unresolved long-term stress or post-traumatic stress and the subsequent cortisol flooding of the brain [6, 7].

— Changes in energy metabolism and disruptions of the circulation in various areas of the brain, and in particular in the left hippocampus, cause depression [6].

Neuroplasticity refers to the ability of the brain to structurally change or regenerate itself via neurogenesis. Neuroplasticity is essential to human health [6].

Stress-induced inhibition of neurogenesis may even result in a volume loss of brain substance in depressive patients, as shown in magnetic resonance imaging (MRI) studies [6—8]. Such volume losses in the brain are reported to be reversible by stimulating neurogenesis, e.g., by means of placebo application, imagery, psychotherapy, or certain pharmaceuticals [6].

In the following, we would like to add another, hitherto unnoticed factor to the previously described complex psychosomatic, psychoneuroimmunological, and neurobiological study of the pathogenesis and, therefore, the treatment of depressive patients: The Consequences of Chronic Co-morbidity of Low Blood Pressure and Cervical Spine Syndrome:

patients of the naturopathic-oriented In NaturMed Hot Springs and Health Resort Davutlar (Western Turkey) who routinely received a relaxation blood pressure test [9, 10] at least 6 times as part of their Asclepian treatment, we found that more than 40% of those tested had low blood pressure (resting systolic blood pressure of <100mmgHg). In these low blood pressure patients the predominant diagnosis on which their primary care physicians had based their referrals were burn-out syndrome, overstress syndrome, chronic fatigue syndrome, sleep disorders, and, mainly, depression, in some cases with a history of long-term antidepressant therapy that had not achieved the desired outcomes. During history taking upon admission to the NaturMed Health Resort, we determined in these patients, in addition to their measured low blood pressure, primarily depressive symptoms, cervical spine syndromes with major discomfort of the neck muscles, chronic fatigue, worsening of symptoms in the morning ("morning low"), head discomforts and vertigo.

Huep [11] described the symptoms of low blood pressure patients as follows (these observations have since been confirmed by many other authors [9, 12, 13]: Fatigue, low achievement, irritability, dampened or anxious exhaustion, depressive moods, narcoleptic-like bouts of sleeping during the day (in particular on monotonous or hot days), cold feet and hands, breaking out in sweats, anomia, occasionally also temporary impotence and fainting, palpitations, other sensations in the region of the heart, extrasystoles and feelings of fear related to the heart, feelings of choking, «inability to take a deep breath», sigh breath, forced yawning, hyperventilation up to hyperventilation tetany, food intolerances, feelings of fullness, diarrhea, constipation, undifferentiated head discomforts, as well as cervical spine syndrome associated with tension in the neck, pain in the back and the extremities.

Reiner and Hecht [14] described a syndrome of «morning lows», in which patients have difficulties getting up, do not feel rested, and have trouble starting their daytime activities. Also, specific sleep disorders were found in low blood pressure patients. However, one peculiarity was observed as well [11, 14]: Not all patients with low blood pressure show the symptoms described. Some do not experience these discomforts at all, others only experience them in the morning, and yet others experience them all day long [14]. Why these differences are observed in persons with very low blood pressure has not yet been scientifically explained.

Methodology

All exams and tests were carried out during Asclepian treatments in the privately run NaturMed Hot Springs and Health Resort Davutlar (Western Turkey). This Asclepian treatment (not drug-based) consists of a chronopsychophysiological program, the main components of which are a regular sleeping-waking cycle, physical activity (hiking in the mountains and along the beach), a healthy diet, supplementation of micronutrients, relaxation, meditative breathing, different forms of massage, group dynamics, hot and cold baths, and imagery, and it offers essentially the same conditions for every patient. Since 2004, the relaxation blood pressure test has been routinely administered to each patient as a diagnostic and therapeutic measure at least six times.

The relaxation blood pressure (BET) test is done as follows: First, the patient is instructed to enter a state of relaxation by closing his or her eyes and mentally controlling his or her rhythmic breathing for 10 minutes. During this period of relaxation, the blood pressure is taken in the left upper arm in 1 minute intervals using a low noise automatic device (Omron comfort M8). The cuff used was an upper arm cuff for arm circumferences of 22 to 42 cm (Omron hard case cuff) that does not painfully squeeze the arm. From these measurements over time the baseline and resting blood pressure (the lowest value of systolic pressure of the final five measurements) can be derived. In this way the true resting blood pressure without masked interferences (such as the «white-coat effect») is obtained. Patients who received blood pressure lowering medication or other medication were excluded. From the group of patients we selected those having a resting systolic blood pressure of <110mgHg. There were several variations of the exams.

Variation 1

In patients with a resting systolic blood pressure of <110mmHg treated according to variation 1 a structured history was taken following the relaxation blood pressure test in order to record the following symptoms that in the previous 2.5 years had been observed most frequently in patients at the NaturMed Health Resort in association with low blood pressure:

1. «Morning low» syndrome: Problems in getting up, a need to sleep longer (which aggravates this state), feeling of never being fully rested, fatigue and exhaustion.

2. Lack of drive, strongly diminished motivation, in particular after rising in the morning, chronic fatigue.

3. Depressive symptoms of varying intensity, in part associated with world-weary thoughts. In some cases suicidal thoughts («I don't want to go on living like this»).

4. Vertigo, problems in maintaining balance, dizziness in association with high temperatures, low air pressure and monotony, and when changing position (in particular when getting up in the morning and after heavy meals).

5. Headaches of all types and feelings of emptiness in the head («like cotton in my head»).

6. Symptoms 1-5 occurring in the morning only.

7. Symptoms are occurring all day long, or there are no discomforts at all.

8. Cervical spine syndrome with tension and/or pain in the neck region.

9. Meteorosensitiveness, in particular in changing weather conditions and when air pressure is low.

10. Sleep disorders, in particular night-time waking with tachycardias.

These exams were done on patients of the naturopathic NaturMed Health Resort Davutlar (Western Turkey) who stayed there between October 2006 and October 2007. Included in the exams done according to this variation were 356 patients out of 864 patients who had a BET done, and whose resting systolic blood pressure was <110mmHg. These were 41.1% of BET tested patients, comprising 129 men (36.2% and 227 women (63.7%). The age range of this population was 20 to 89 years. The mean age was 53.6 ± 13.4 years. The age distribution was a normal (Gaussian) distribution.

Variation 2

In variation 2 we found 56 patients (40.5%) with a resting systolic blood pressure of <110mmHg among 138 patients who had had the BET administered in the spring of 2009. With these patients we used the German variation of the Hospital Anxiety and Depression Scale (D-HADS). The Hospital Anxiety and Depression Scale (HADS; Zigmond und Snaith 1983) is a well-established tool for the self-assessment of mild and moderate forms of anxiety and depression which has been designed for use in somatic patients. The German version (D-HADS) was validated by Herrmann et al. [15] and is available as a testing manual (Herrmann et al. 1995). Assessment follows this scheme (Herrmann et al. 1995): HADS Depression values: negative (0—7), ambiguous (8—10), positive (≥11).

Other than this the same treatment conditions applied to the patients of variation 2 as to all other patients.

Variation 3

In a small sample of 13 patients, all of them participants in an Asclepian treatment in the fall of 2009, who showed significant problems in the mornings («morning low» syndrome) and were symptom-free in the afternoons, we measured their blood oxygen saturation (SpO₂) in their left ring fingers at two different times during the day, using an «Onyx II» oximeter.

Statistics

Significance tests were done using the Wilcoxon test for correlated samples. All calculations were done using the statistics software package SPSS 12.0.1.

Differences with p-values of p < 0.05 (*), p < 0.01 (**), or p < 0.001 (***) were considered significant. Differences with a p-value of p > 0.05 were deemed not significant (n. s.).

Results

Test Variation 1

1.1 Mean blood pressure values

There was a mean difference of about 17 mmHg between the baseline and the resting blood pressure for the entire group (Wilcoxon test p < 0.0001, men: 18 mmHg, women: 16 mmHg). The mean baseline systolic values are in the normotension range, and the mean resting systolic relaxation values are in the hypotension range. The diastolic blood pressure values are very low at baseline already and thus are lowered by only 5mmHg during the BET.

1.2 Concomitant clinical symptoms in low blood pressure

1.2.1 Occurrence of symptoms

As seen in our studies, 20.2% of low blood pressure patients had none of the typical symptoms. In 34.3%, symptoms were only seen in the mornings, and 45.5% experienced symptoms all day long.

1.2.2 Details of symptoms in patients with a systolic blood pressure of < 110mgHg

An overview of these results and the corresponding resting blood pressure values are given in Table 1. All symptoms are accompanied by hypotension of nearly the same level.

Of the 269 low blood pressure patients who experienced depressive symptoms, 101 (37.5%) had been treated before their treatment at NaturMed Health Resort with antidepressants for a duration of 0.5 to 12 years, with frequently switched drugs and very limited success.

All these drugs were discontinued starting on their first day at the Health Resort, without any signs of withdrawal. In 31 of these patients treated with antidepressants restless legs syndrome was observed, which we interpreted to be a side effect of the antidepressant therapy because this symptom disappeared after discontinuation of the antidepressants.

In the brief routine interviews conducted at the end of the Asclepian treatment (after 2 to 4 weeks of treatment) 265 patients reported that their depressive symptoms had partially or completely disappeared. Our

Table 1. Percentage of clinical symptoms of	of the entire group	(<i>n</i> =356) and th	ne associated	mean values	and standard
deviations for systolic and diastolic blood	pressure values				

Symptom	Frequency of concomitant	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)		
	clinical symptoms (%)	Mean	SD	Mean	SD	
«Morning low» syndrome	78.6	97.4	7.47	62.7	7.76	
Chronic fatigue,						
lack of drive	78.6	97.4	7.47	62.7	7.76	
Depressive symptoms	75.6	97.4	7.47	62.7	7.76	
Vertigo	77.5	97.4	7.49	62.8	7.67	
Headache, empty feeling in the head	77.5	97.5	7.46	62.8	7.67	
Cervical spine symptoms	84.5	97.6	7.48	62.7	7.67	
Meteorosensitiveness	80.9	97.5	7.51	62.7	7.82	
Sleeping disorders	47.5	96.8	7.71	62.2	7.67	
Tinnitus	28.3	96.9	8.03	62.0	7.83	
Migraines	24.1	95.1	8.44	61.6	7.26	

Table 2. D-HADS values of 56 patients with low blood pressure and some concomitant symptoms of low blood pressure

Symptom	Number	Percentage (%)	
HADS-value > 11, positively depressed	48	85.7	
HADS-value 8—10, not clearly depressed	2	3.6	
HADS-value 0—7, not depressed	6	10.7	
«Morning low» syndrome	44	78.5	
Chronic fatigue, lack of motiviation	46	82.1	
Head aches and head related discomforts	46	82.1	
Sleeping disorders	32	57.2	

Table 3. D-HADS scores at the beginning of the Asclepian treatment and after 10 to 13 days of treatment, individual examples

Patient code	Age	Sex	BP (mmHg) before treatment	D-HADS score before treatment	Treatment days	BP (mm Hg)	D-HADS score after 10—13 days of treatment	Antidepressant use before treatment
NS	47	f	95/63	18	13	89/66	3	4 years
SV	48	f	97/69	17	13	102/63	5	9 years
O.S	59	m	98/62	20	10	103/62	7	8 years
K-U.	37	f	96/70	15	10	81/58	3	alcoholism
AK	54	f	101/71	17	10	93/72	8	5 years
BE	46	f	84/52	17	10	88/50	4	none
UM.	68	f	90/60	19	10	92/52	6	none

observation of the patients' behavior during their treatment and conversations with them confirmed these assessments. Only four male Turkish patients (aged 45, 49, 51 and 54 years) did not show any improvement.

Test Variation 2

Test variation 2 was used to verify results from variation 1 with a different method for determining the depressive symptoms, i. e., using the D-HADS instrument (Table 2).

To this end, in April and May of 2009, 56 patients (36 women and 20 men) who had a systolic blood pressure of <110mmHg out of a group of 138 patients who had received a daily relaxation blood pressure test were tested.

Mean resting systolic blood pressure (n=56):

93,3±8,3 mm Hg

Mean resting diastolic blood pressure (n=56): 62,9 \pm 7,8 mmHg

Note that in this group 27 patients (56.7%) of the 48 depressed patients had been treated without signifi-

cant success for 2 to 12 years with various antidepressants. In some of these patients side effects occurred, mainly manifesting as restless legs syndrome (in 10 of the 27 patients treated with antidepressants).

For 7 of these patients we repeated the D-HADS assessment between day 10 and day 13 of their treatment at the Resort (Table 3).

Within 10 to 13 days of the Asclepian treatment D-HADS scores were reduced for the 7 patients shown, with a tendency towards normal scores. The resting systolic blood pressure values did not change significantly during this time. In all 7 patients the cervical spine symptoms had disappeared.

Test Variation 3

In order to verify the suspected cerebral hypoxia (cerebral microhypoxia) as a consequence of the concomitant occurrence of low blood pressure and cervical spine syndrome, we studied blood oxygen saturation in a small sample of 13 low blood pressure patients who suffered significantly from concomitant clinical symptoms in the morning and performed well in the afternoons. Measurements were done:

1. in the mornings between 6:00 a.m. and 6:30 a.m. (immediately after waking)

2. in the afternoons between 3:30 p.m. and 4:00 p.m.

In computing the median of these data it was found that the morning resting blood pressure was 91/60mmHG and the evening resting blood pressure was 94/60mmHg. Oxygen saturation showed a median of 92% in the morning and of 98% in the afternoon. After waking, all patients felt exhausted, tired, depressed, and unmotivated, but in the afternoon they all were relatively well to very well and able to perform.

Discussion

The results presented here reveal the dynamic interactions of several functional systems in pathophysiological processes. Based on practical experience that has been confirmed by these results, low blood pressure has been considered the cause of specific concomitant clinical symptoms [9, 11, 16].

However, it had remained unclear why not all patients with low blood pressure exhibited these concomitant clinical symptoms. We also were not able to find quantitative data on the prevalence of these concomitant symptoms in the relevant literature. For the first time, we were able to present figures, namely: Only 21.5% of patients were without concomitant symptoms.

While these figures may not be representative, they still give us an idea of the prevalence of the concomitant symptoms of low blood pressure, which always included depressive symptoms. What is certain is the following:

Patients who were affected in the morning or all day long (a total of 79.5% of all those studied with low blood pressure) complained about a high level of suffering. They felt temporarily or permanently stressed, very exhausted and experienced an associated depressed state and reduced quality of life. As we were able to show as well, the concomitant clinical symptoms were actually associated with a resting systolic blood pressure of <110mmHg. They were only rarely observed at a higher resting systolic blood pressure. Of the concomitant symptoms in our study, those symptoms were predominant that are associated with depression. The physicians who treated these patients before their Asclepian treatments also interpreted these symptoms as signs of depression and prescribed antidepressants (in 37.5% of the cases in our study variation 1, in 56.2% of the cases in study variation 2).

We confirmed the co-morbidity of low resting systolic blood pressure (<110mmHg) and depressive symptoms both with structural history taking and, in one group, with a specific test, the D-HADS. What was most conspicuous, however, was that during the 2 to 4 weeks of treatment the depressive symptoms as well as the concomitant clinical symptoms of low blood pressure were reduced in most cases and fully disappeared in some. Blood pressures, on the other hand, remained low. Consequently, there had to be other factors involved that we were able to influence with our Asclepian treatment.

Our earlier observations that changes in the cervical spine may play a role in this have been confirmed by our results. The reported vertigo, head-based discomforts and feelings of emptiness in the head, in particular in an environment of high temperature led to the assumption that cervical spine symptoms and low blood pressure may lead to repeated short- or longer-term cerebral hypoxias (cerebral microhypoxias). These may result in disturbances of the cerebral circulation as well as the cerebral neurotransmitter and metabolic balance, which in turn may be reflected by depressive symptoms. Our patients felt cerebral circulation disorders most strongly when air pressure was low, in foehn conditions, and when thunderstorms were approaching. More than 80% of our patients reported meteorosensitiveness. A known phenomenon is the so called «foehn rausch» [17] which supposedly results from disturbances in the cerebral transmitter system.

Patients with concomitant symptoms of low blood pressure suffer most from them right after waking up. Apparently, the reduced oxygen saturation in blood plays a role in this, as evidenced by our studies in 13 patients who presented as «two day-time personalities» [14], i. e. they were depressed in the mornings and active or even hyperactive in the afternoon.

Therefore, it can be assumed that the relatively low oxygen saturation in blood triggered the feelings of exhaustion, depression, and lack of motivation in the mornings. The full day-time program of the Asclepian treatment then stimulated the patients, resulting in their oxygen saturation reaching normal levels that were reflected in their being well or even very well. Repeated cerebral micro hypoxias as a consequence of concomitant low blood pressure and cervical spine symptoms would also explain why, in the majority of our patients, a reduction of depressive symptoms by means of our Asclepian treatment could be shown: They hiked for 1-2 hours daily, took hot and cold baths, received massages and PPT (pulsating pneumatic therapy) of the neck and shoulder region, did aqua aerobics, were instructed on how to best use their pillows for sleeping and learned to relax and to breathe meditatively, in short, they were being de-stressed.

Suggestions of a possible connection between low blood pressure and depression were also reported by the Japanese-American group of researchers Yamaka et al. [18]. They measured their subjects' blood pressures every 30 minutes around the clock on 7 continuous days. In addition to the usual tests, scores on the Geriatric Disease Scale (GDS), which contains a subscale for depression, were repeatedly determined in more than 140 subjects and for the first time in 172 subjects.

The authors found a weak positive (Z) association between the MESOR of systolic blood pressure and GDS scores (r=0.171, p=0.025) as well as an association between the circadian amplitude of the heart rate and GDS scores (r=0.25, p=0.005).

In our studies as well the main parameter for the relationship between symptoms of depression and low blood pressure was the resting systolic blood pressure.

Pathophysiologically, «primary idiopathic» essential hypotension is described as a dysregulation with insufficient central and peripheral adrenergens and symptoms of sympathetic adaptation and circulatory regulation issues [19]. It is said that sympathetic activity is suppressed and the vasomotor balance has been shifted towards parasympathetically stimulated responses.

Another potential Pathophysiological factor we would like to list here, referring to Kuklinski [20, 21] is nitrosative stress. This might be responsible for the concomitant symptoms we and others [11, 14] observed in low blood pressure patients. Kuklinski [21] observed in his clinical practice that «hypotension with systolic values of less than and around 100mmHg signals nitrosative stress».

Nitrosative stress is the term used to describe a chronic excess of NO in the human body, which often is associated with oxidative stress (O_2^-) [20, 21].

Nitrosative and oxidative stress, i.e., the hyperoxide anion O_2^- and nitric oxide NO interfere with mitochondrial activity [22, 23].

If NO is chronically increased, according to Kuklinski it will induce a release of mitochondrial cytochrome G and thereby apoptosis [5]. The resultant lack of ATP activates the glutamate receptor, with a subsequent increase of intracellular Ca^{++} and additional stimulation of «NO synthesis and super oxide formation».

According to Kuklinski [21], NO and O_2^- form peroxynitrite (ONOO⁻) which is neurotoxic. It «irreversibly inhibits mitochondrial enzymes and oxidizes many metabolites such as cholesterol, vitamin C, uric acid, coenzyme Q10, SH containing enzymes, polyene fatty acid» [21], alpha liponic acid and others. Peroxynitrite early harms the axons of neurons and, therefore, interferes with neurotransmitter signaling [21].

This «sets into motion a vicious circle». Warnke [24] found that the stimulation of the hyperoxide anion O_2^- and nitric oxide NO among others damage the mitochondrial genome, the nuclear genome, and the membranes.

Kuklinski [20, 21] points to the importance of defects in the «joints of the cervical spine» which, according to his observations, lead to recurring cerebral hypoxias and may promote neurological-psychiatric disorders. Chronic recurring cerebral hypoxias, according to studies by Kuklinski cause an increase in the synthesis of nitrosative and oxidative stress.

Our results show that 84.5% of our patients had cervical spine symptoms. According to observations by Kuklinski [21] patients with chronic sleep disturbances and with recurring NO peaks do not feel refreshed when waking. They also, in case of cervical spine issues, exhibit a long «warming up» time in the morning. In this context the «morning low» syndrome (78.6%) and their reduced oxygen saturation in blood in our patients is to be mentioned.

Finally, Kulinski [21] found that chronic nitrosative and oxidative stress (spreading throughout the body) were followed by migraines, chronic fatigue syndrome, chronic exhaustion, depression, Parkinson's disease and others. We observed the same pathological symptoms in some of our patients.

According to Kuklinski [21], the consequences of chronic nitrosative stress will result in massive losses of vitamin B12, potassium, and magnesium. He reported that these pathological symptoms could be remedied by exercise (Nordic walking, running, jogging, etc.), switching to a low carbohydrate diet and individually differentiated administration of various micronutrients (in particular vitamins, enzymes, and minerals). Kuklinski [21] also found that the majority of patients experiencing the listed deficits were not responsive to medication. These and our findings would explain why antidepressant treatments frequently fail [4].

Chronic oxidative and nitrosative stress leading to disturbances in the mitochondrial system and being aggressive against cells might also explain the inhibition of the neurogenesis described by Rüegg [6] and the loss of cerebral substance observed in depressed patients.

In view of our results and in those of the neurobiological understanding of depression according to which depression significantly modifies cerebral neuroplasticity, as well as in light of Kuklinski's results [20, 21], at the time of the diagnosis of a depressive disorder it would be absolutely necessary to supplement the psychological tools with the determination of oxidative and nitrosative stress levels, measuring the resting systolic blood pressure, sleep analysis, an examination of the cervical spine, and measuring oxygen saturation in the blood. Accordingly, a non drug treatment should be initiated, e. g. a treatment such as our rather successful Asclepian treatment.

In case of severe depression, breaking the motivational deficit with psychotherapy is indicated. Subsequently, it should be treated with the Asclepian treatment, including psychotherapy and «talking medicine» [6], just the same as milder cases of depression.

We think that our studies and experience presented here have shed light on a hitherto unknown gap in the pathophysiology and therapy of depression, and that we have shown how to close that gap.

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