Psychosomatic Medicine and General Practice
Vol. 5 No. 1 (2020)
DOI: 10.26766/pmgp.v5i1.229

A psychosomatic approach to the diagnosis and treatment of anxiety in patients with chronic noncommunicable diseases

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Background. Anxiety is a normal protective mechanism that a person acquired during evolution and is the very first mental reaction that occurs in response to a disease or precedes it. When anxiety becomes long-term and pronounced, it is anxiety as a disorder that negatively affects a person's quality of life, disrupting his physical, mental and social functioning.

The early diagnosis and treatment of anxiety in patients with chronic noncommunicable diseases (NCD) is important for preventing chronic and somatization of mental disorders, reducing and preventing complications of NCD.

At the primary care level, naturopathic drugs occupy an important place in the treatment of subclinical anxiety disorders or somatized anxiety disorders. A number of clinical studies prove the anxiolytic and anti-stress effect of ashwagandha extract L-thianine and passiflora extract (Passiflora incarnata), which were combined in the phytotherapy complex Anxiomedin®.

Methods and materials. An 4-week study tested the efficacy and safety of Anxiomedin in the treatment of psychosomatic manifestations of anxiety in 75 adult ambulatory patients with NCD. Patients were examined according to the HADS Hospital Anxiety and Depression Scale, a four-dimensional questionnaire for assessing distress, depression, anxiety and somatization 4DSQ, the Sax-Sydney SSCT method of incomplete sentences; blood pressure (BP) and pulse were also monitored.

Results. At 4 weeks of therapy, patients with NCD and subclinical anxiety had a reduction: somatization on the 4DSQ scale (-57.7%), anxiety on the HADS scale (-58.6%), conflict index according to the SSCT method (-42.3%) , sympathicotonia (decrease in heart rate by 24.4%). Also according to the SSCT method, significant conflict zones that have undergone a significant reduction in the course of therapy were: attitude to the future ($p < 0.01$); fears and anxieties ($p < 0.01$); attitude to the disease ($p < 0,01$); attitude to himself ($p < 0,05$). No significant side effects were detected during the study.

Conclusion. There is a two-way link between anxiety and NCD regarding the onset and development of mental and physical disorders. In the treatment of subclinical and somatized anxiety, especially in primary care, naturopathic drugs, such as Anxiomedin, have proven to be effective and safe.

Background

Recent studies show that the reactions to allostatic overload (*Fig. 1*) [1] and stress go beyond

normal with the formation of maladaptive reactions such as neuroticism (neurotic reactions), somatization (psychosomatic disorders), and behavioral disorders (psychopathic and/or addictive behavior) with a predominance of permanent distress, anxiety, and depression in the mental state of a person.

Figure 1. *Allostatic loading according to Diagnostic criteria for psychosomatic researches.*

Anxiety, which includes emotional, behavioral, somatic, and cognitive components, like depression, can be either a single symptom or a manifestation of a number of mental disorders. Anxiety disorders cause a significant increase in health care costs in the world, primarily at the individual level rather than at the population level due to the predominant predisposition of many patients to their hyponosognosia and underestimation of negative somatic and psychosocial consequences [2].

They are common in modern societies and rank 6th in the importance of negative non-fatal health consequences [3]. Thus, for the period 2005-2015, their number increased by 14.9%, reaching in 2015 about 264 million (3.6%) according to the WHO. The Institute for Health Metrics and Evaluation (IHME) reported 3.83% of anxiety disorders in 2016. The difference in the prevalence of anxiety disorders worldwide is due to the significant uncertainty of diagnostic approaches, so the current global prevalence of anxiety disorders at the level of 7.3% (4.8% to 10.9%) was proposed [4]. In general, more than 28% of people have experienced symptoms of anxiety disorder at least once in their lives [5].

WMHS analysis has shown that childhood disorders and mental disorders at an early age increase the risk of such conditions in later life [6]. In adults, there is a strong association between anxiety disorders and subsequent coronary heart disease [7], stroke, and diabetes [8]. Patients with Metabolic Syndrome (MS) had a high level of reactive and personal anxiety, and the number of people with high reactive anxiety was twice as high in the group of Premetabolic syndrome (57.35%) than in the group of formed MS (26,36%) ($p = 0.014$). In the process of forming the metabolic syndrome in the absence of a clearly defined somatic pathology (hypertension, diabetes, coronary heart disease, etc.) there is a high level of psychological discomfort at the reactive level, but not the personal level. Reactive anxiety as a reflection of the subjective response to emotions of tension, anxiety, concern with the corresponding activation of the sympathetic-adrenal system, contributed to the further development of MS. The presence of somatic multimorbidity in MS patients was associated with an increase in persistent personal anxiety (fears about health, future), but partially deactivated current events in their imagination, helping to reduce reactive anxiety [9]. We also observed a combination of anxiety and fear, with fears mainly related to interpersonal relationships in Premetabolic syndrome, and directly related to health in MS. Patients with Premetabolic syndrome often indicated fear of loneliness, incompetence, betrayal of loved ones, serious illness; for patients with MS fear of loneliness, helplessness, serious illness, death were inherent. Such psychopathological manifestations have been associated with a decrease in the quality of life and working capacity of patients with MS [10].

A similar close association between somatization and disability (41.8% at baseline; 31.7% after one year of follow-up) was found in a survey of 1,545 patients with anxiety and depressive disorders in the NESDA longitudinal study. Delayed functional recovery was inherent primarily in patients in the

second half of life [11]. At present, the search for the exact mechanisms of such psychosomatic relationships, methods of clinical assessment of anxiety disorders, and adequate interventions through psychobiological, behavioral, and purely clinical studies is still ongoing [12].

Usually, anxiety for a person is a normal defense mechanism, which was received in the process of evolutionary development. Normally, it is transient and controlled. But as soon as anxiety becomes long-lasting, expressed in its intensity, disrupts social functioning, and causes unpleasant physical (somatic) feelings, we can talk about anxiety as a disorder. In addition, anxiety is one of the first mental reactions that occur to the development of the disease or precedes it.

Bilateral effects of anxiety/panic and somatic disorders described by A. E. Meuret and co-authors (2020) [13]: under the influence of constant environmental and dispositional risk factors, mental and somatic disorders interact through biopsychosocial mediators. Moreover, such mediators as signs of an unhealthy lifestyle (hypodynamics, obesity, smoking), the predominance of sympathicotonia, and the presence of oxidative stress and pharmacotherapy are also bilaterally unchanged. Anxiety/panic contributes to the development of NCDs due to the patient's anxious attitude "anticipation of anxiety" with a corresponding physiological but excessive reaction "fight, flight or freeze"; due to hyperactivity of the HPA axis and the inflammatory reaction, including due to increased synthesis and circulation of proinflammatory cytokines (*Fig. 2*).

Figure 2. *Influence of anxiety/panic on the formation of NCDs (modified by E. Meuret et al. (2020))*

In turn, NCDs further contribute to the development of anxiety/panic due to low adherence to therapy with subsequent distress and catastrophic symptoms of the somatic disease, leading to hyperventilation and anxiety of asphyxia (*Fig. 3*).

Figure 3. *Influence of NCDs on the formation of anxiety/panic (modified by E. Meuret et al. (2020)*

Anxiety negatively affects a person's quality of life, disrupting physical, mental, and social functioning. Thus, early diagnosis and treatment of anxiety disorders are important components of patient care, aimed at preventing chronicity and somatization of mental disorders.

According to international standards of care for patients with anxiety disorders, the optimal treatment tactics are a combination of pharmacotherapy and psychotherapy. According to the NICE QS53 (2014) quality standard, psychotherapy is considered to be the first line of treatment for anxiety disorders. Even low-intensity measures, including self-help and high-intensity psychological treatments, are effective. It is also emphasized that people with anxiety disorders should not be prescribed benzodiazepines or neuroleptics unless there are specific clinical reasons [14].

On the one hand, in the case of mild anxiety disorders, data demonstrating cost-effectiveness remain relatively limited. Although mild anxiety disorders certainly concern, responses to anxiety are often adaptive, and supportive interventions are hypothetically more economically burdensome than intensive care for acute conditions. On the other hand, anxiety disorders are associated with significant subsequent comorbidity and morbidity. Therefore, early and reliable intervention can be a cost-effective option. Finally, the decision on the optimal determination of diagnostic and intervention thresholds is one that requires empirical verification. Similarly, studies of early interventions for anxiety disorders are appropriate to determine whether it has a positive effect on the occurrence, persistence, or severity of secondary disorders [5,15].

Naturopathic drugs take a prominent place in the treatment of anxiety disorders, mainly subclinical level or somatized anxiety disorders, especially at the level of primary care [16].

Methods and Materials

We conducted a 4-week comparative randomized post-marketing study of the efficacy and safety of the Anxiomedin® phytotherapeutic complex in the treatment of psychosomatic anxiety in adult outpatients with chronic non-communicable diseases (CNCDs). Subject to informed consent, in compliance with the principles of bioethics and deontology, the study involved 75 adult patients with NCDs and pre-nosological anxiety disorders with mental and somatic anxiety symptoms, who were randomized on a 2:1 ratio to the main and comparative groups, where 50 patients (>65%) received Anxiomedin 1-3 capsules per day depending on the severity of clinical symptoms. At the end of the study, patients in the comparison group were treated as needed to reduce anxiety symptoms.

Inclusion criteria:

- age 18-70 years;
- CNCDs of mild/moderate severity;
- ≥ 6 points on the Psychosomatic Orientation Questionnaire;
- ≥ 8 anxiety scores on the Hospital Anxiety and Depression Scale (HADS), the number of points on the anxiety subscale is higher than on the depression subscale.

Exclusion criteria:

- severe uncontrolled CNCDs;
- for HADS anxiety/depression ≥ 15/15 and/or suicidal tendencies;
- pregnancy, breastfeeding;
- idiosyncrasy to individual components of the drug.

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Patients were verified according to Diagnostic criteria for psychosomatic studies of aberrant behavior and clinical manifestations [1]. They were examined on the hospital anxiety and depression scale HADS, a four-dimensional questionnaire to assess distress, depression, anxiety, and somatization 4DSQ, the method of incomplete Sachs-Sydney sentences SSCT [17-21]; systolic and diastolic blood pressure (BP), and pulse were monitored.

Mathematical and statistical data processing was carried out by the method of variation statistics with the estimation of the distribution law using the Kolmogorov-Smirnov criterion; Fisher's criterion (φ *) and Pearson xi-square (χ2) were used to assess the significance of the differences.

Results and discussion

The age of the surveyed persons ranged from 21 to 68 years, with a predominance of middle-aged persons (31–40 years - 46.7%; 41–50 years - 29.3%). The average age of the examined main group (MG) was 38.4 ± 7.1 years, the comparison group (CG) - 36.8 ± 7.4 years. By gender structure, the main group consisted of 28 women (56.0%) and 22 men (44.0%), respectively. The comparison group consisted of 15 women (60.0%) and 10 men (40.0%). A significant difference between the groups by average age and sex was not determined ($\chi 2emp < \chi 2crit$, $p \leq 0.01$), which was provided by the criteria for forming a sample for inclusion in the study. The obtained data testified to the homogeneity of the sample, which made it possible to study and analyze the clinical and psychopathological features of patients.

Patients in both groups received standard treatment for hypertension (20 individuals, 26.7%), coronary heart disease (19 individuals, 25.3%), type II diabetes mellitus (15 individuals, 20.0%), and gastric ulcer/duodenum (9 individuals, 12.0%), rheumatoid arthritis (7 individuals, 9.3%) and other chronic non-communicable diseases (5 individuals, 6.7%). Aberrant behavior of the examined patients indicated the presence of anxiety adjustment of the subclinical level, which was further confirmed by the data of the examination on the Hospital scale of anxiety and depression. Each patient has one or more manifestations of aberrant behavior (multiple choice) (*Table 1*).

Aberrant behavior	Groups			
	MG (n=50)		CG (n=25)	
	N	%	N	%
Hypochondria	11	22,0	8	32,0
Nosophobia	7	14,0	3	12,0
Thanatophobia	8	16,0	5	20,0
Healthy anxiety	7	14,0	3	12,0
Stable somatization	34	68,0	16	64,0
Conversion symptoms	6	12,0	2	8,0
Reaction to the anniversary	3	6,0	2	8,0
Denial of the disease	2	4.0	1	4,0

Table 1. *Distribution of the examined persons by aberrant behavior according to the Diagnostic criteria for psychosomatic researches (n = 75)*

In most patients with CNCDs there were pronounced manifestations of persistent somatization of anxiety (68.0% and 64.0%, respectively), hypochondria (22.0% and 32.0%, respectively), thanatophobia (16.0% and 20.0%, respectively) and nosophobia (14.0% and 12.0%, respectively). Instead, the level of healthy anxiety (*Fig. 4*) reached 14.0% and 12.0%, respectively.

Figure 4. *Non-pathological anxiety according to Diagnostic criteria for psychosomatic research*

According to the results of the 4-week application of the phytotherapeutic complex Anxiomedin®, we noted a decrease in anxiety on the Hospital scale of anxiety and depression in MG compared with CG at the 2nd week of therapy at the level of the trend (-4.6 points), its significant reduction at the 4th weeks (-8.6 points; p <0,05) (*Fig. 5*).

Figure 5. *Anxiety reduction according to the Hospital Scale of Anxiety and Depression*

The reduction of depression according to HADS with Anxiomedin was not significant, remaining at the trend level (-3.3 points on FU) (*Fig. 6*).

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Figure 6. *Reduction of depression on the Hospital scale of anxiety and depression*

The reduction in the total number of symptoms of the main group during Anxiomedin therapy was analyzed in a four-dimensional questionnaire to assess distress, depression, anxiety, and somatization of 4DSQ. Reduction of anxiety in the 4th week was 41.3%, distress - 55.4%, somatization - 57.7% (*Fig. 7*). Moreover, the most pronounced was the reduction of somatization: -3.5 points on the 2nd week of therapy; -12.7 points at the 4th week ($p < 0,01$).

Figure 7. *Reduction of individual domains of the 4DSQ scale during Anxiomedin therapy*

In the 2nd week of Anxiomedin therapy, there was a steady tendency to decrease SBP, DBP, and cardiac rate with a subsequent significant decrease ($p < 0.05$) of these indicators at 4 weeks, with a further decrease in heart rate to FU. Which corresponded to the normalization of the activity of the sympathoadrenal axis by reducing sympathicotonia [12] (Fig. 8).

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Figure 8. *Reduction of sympathicotonia during Anxiomedin therapy*

The conflictogenity index according to the method of incomplete Sachs-Sydney decisions was reduced from 17.4 points to 10.0 points (Fig. 9) with the following most significant conflict zones that have undergone a significant reduction in the course of therapy: attitude to the future ($p < 0,01$); fears and anxieties ($p < 0.01$); attitude to the disease ($p < 0.01$), to oneself ($p < 0.05$), to the family ($p < 0.05$) and to the mother ($p < 0.05$).

Figure 9. *Reduction of conflict-generating zones according to the Sachs-Sydney method*

Thus, the most significant changes in the psychopathological condition of patients with CNCDs and subclinical anxiety during 4 weeks of Anxiomedin therapy were reduction: somatization on the 4DSQ scale (-57.7%), anxiety on the HADS scale (-58.6%), conflictogenity index according to the SSCT method (-42.3%), sympathicotonia (decrease in heart rate by 24.4%) (Fig. 10). No significant side effects were detected during the study.

Figure 10. *Final efficacy indicators of Anxiomedin in patients with CNCDs and subclinical anxiety*

Conclusion

There is a two-way link between anxiety and CNCDs regarding the onset and development of mental and physical disorders. Early diagnosis and treatment of anxiety in patients with CNCDs are important for the prevention of chronicity and somatization of mental disorders, reduction, and prevention of complications of CNCDs itself. In the treatment of subclinical and somatized anxiety, especially in primary care, naturopathic drugs such as Anxiomedin, which have proven their effectiveness and safety, occupy a prominent place.

Additional information

Conflict of interests

The current study was funded by LLC Nurtimed.

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