Review
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How can we improve clinical outcomes by understanding the inseparability of mind and body?

Kako možemo poboljšati kliničke ishode razumijevanjem nerazdvojivosti uma i tijela?

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Summary

We have experienced that very often the medical outcome does not depend exclusively on laboratory results or clinical findings, but also on the invisible part of every human - his mind. We focused on reviewing previous studies on the inseparability of mind and body in different medical specialties, improvement of communication skills and understanding human psychology in everyday clinical practice. The psychosomatic effects in cardiology, gastroenterology, diabetology and dermatology that we adduced in our review article requires a comprehensive personalized assessment that takes into consideration the interaction of the mind, body, and social environment. Mentioning many medical specialties, we can conclude that a psychosomatic approach and given solutions should not be only restricted to psychiatry, medical psychology and psychosomatic medicine, but rather involved into almost any clinical practice.

Key words: psychosomatic medicine, stress, emotions, personalized approach, clinical outcomes

Sažetak

Dosadašnje iskustvo ukazuje nam na to da vrlo često klinički ishod ne ovisi isključivo o laboratorijskim nalazima ili kliničkim znakovima, nego i o onom nevidljivom – umu čovjeka. Usmjerili smo se na prikaze dosadašnjih proučavanja nerazdvojivosti uma i tijela u različitim specijalnostima, unaprjeđenjem komunikacijskih vještina i razumijevanju ljudske psihologije u svakodnevnoj kliničkoj praksi. Psihosomatski učinci unutar kardiologije, gastroenterologije, dijabetologije i dermatologije, koje smo naveli u našem preglednom radu, zahtijevaju sveobuhvatni personalizirani pristup koji uzima u obzir interakcije uma, tijela i socijalnog okruženja. Stoga zaključujemo da psihosomatski pristup i ponuđena rješenja ne bi trebala biti ograničena samo na psihijatriju, psihološku i psihosomatsku medicinu, nego moraju uključiti i kliničku praksu iz gotovo svih medicinskih specijalnosti.

Ključne riječi: psihosomatska medicina, stres, emocije, personalizirani pristup, klinički ishodi

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Introduction

We have experienced that very often the medical outcome does not depend exclusively on laboratory results or clinical findings, but also on the invisible part of every human – his mind. Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.[1] This idea of biological, psychological and social involvement was proposed in 1948 by the first president of the World Health Organization (WHO), Andrija Štampar whose definition of health still today is part of the WHO Constitution. Unfortunately, today we are all faced with the COVID19 pandemic, related stressful life events and unpredictable outcomes. As this all may lead to the impairment of the psychological and social components of health, global uncertainty served us as a motivation for research in the field of psychosomatic medicine and possible solutions for the prevention of disease development or its further

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progression. Wanting to understand the psychological factor, we fully studied related findings from its beginning to today's important clinical and epidemiological research. We focused on the inseparability of mind and body in different medical specialties, improvement of communication skills and understanding human psychology in everyday clinical practice. We offer solutions for physicians who want to improve clinical outcomes through implementing an integrative approach into their daily practice.

Development of psychosomatic medicine

Galen of Pergamon, a Roman physician whose ideas were accepted until the mid-19th century, introduced into medicine the idea that sadness, anger, and fear were the causes of some diseases.[2] In 1637, Descartes influenced the development of Western medicine by separating the self-conscious subject "res cogitans" from the unconscious object, i.e. the human body "res extensa". Over time, Galen's practice began to be neglected and physicians focused on researching exclusively "res extensa". In 1811, Johann Christian August Heinroth became head of the new Department of Psychic Medicine at the University of Leipzig. He considered himself and his colleagues to be "psychic doctors", more precisely, he claimed that they were doctors with great medical, pedagogical, philosophical and theological knowledge.[3] Heinroth first coined an adjective that remained accepted throughout the world - psychosomatic. In 1818, he described that insomnia was caused by psychosomatic sources.[4] German physician Georg Groddeck is considered as the founder of modern psychosomatic medicine. Groddeck published "Psychic Conditioning and Psychoanalytic Treatment of Organic Disorders" in 1917 where he describes that unconscious actions determined how susceptible individuals were to disease development, the nature of the disease, and the possibility of recovery.[5] In 1942, Helen Flanders Dunbar became the first president of the new association - "American Psychosomatic Society" and the first editor of their journal "Psychosomatic medicine". She laid the foundations for research of the relationship between personality types and the development of diseases. Even today, we identify Dunbar's coronary type with the type A personality, which we will clarify in more detail later.[6] In 1977, Science published an article in which George Engel explained that a new biopsychosocial medical model should be pursued. He claimed that in addition to molecular biology, health and disease are also affected by psychological and social factors. He also stated that every doctor has the important role of educator and psychotherapist and that with the knowledge of psychological medicine, not charisma, he can strengthen the relationship with his patient and the patient's faith in healing.[7] These days, when discussing personalized medicine as the most promising model, we must not allow the possible simultaneous development of "depersonalized medicine" by neglecting psychological and social factors.[8]

Stress

Hans Selye was the first who used the word stress in 1936 in the Nature journal when he detailed his well-known general adaptation syndrome. The syndrome contains three phases: the alert phase, the resistance phase, and the exhaustion phase. Alarm is a response to the acute action of a stressor. When the effects of stress are prolonged, the adaptation phase follows, which is manifested by a generalized adaptation syndrome. During the long-term action of stressors, the organism becomes non-resistant and diseases occur due to exhausted adaptive mechanisms. Quantitatively larger and prolonged stressors are called distressors. The strength and duration of distressors are called allostatic loads. American neuroendocrinologist McEwen[9] proposed the formulation of the relationship between stress and disease-leading processes based on the concept of allostasis, the body's ability to achieve stability by changing physiological parameters to meet challenges. Thus, the allostatic load reflects the cumulative effects of stressful experiences in everyday life. When chronic exposure to fluctuating and elevated nervous or neuroendocrine responses exceeds an individual's coping capabilities, allostatic overload occurs.[10] Interestingly, Kiecolt-Glaser et al. proved that a chronic stressor (caregiving for a spouse with dementia) is associated with an impaired immune response to influenza virus vaccination when comparing with matched control subjects. Caregivers showed a poorer antibody response following vaccination as well as lower levels of in vitro virus-specific-induced interleukin 2 levels and interleukin 1 beta levels. These data demonstrate that down-regulation of the immune response to influenza virus vaccination is associated with a chronic stressor in the elderly.[11] We have described the effects of chronic stress, but acute emotional or physical stress can also lead to the development of significant diseases. An interesting epidemiological study was conducted to estimate the number of patients transported to emergency services in 15 major German hospitals for the treatment of coronary heart disease during the one-month period of the FIFA World Cup in Germany. The daily number of patients who visited emergency

services for acute coronary heart disease was significantly increased by six of the seven days of the fight, and it was concluded that cardiovascular events arose due to the excitement of watching World Cup football matches.[12] Another example is the reversible form of takotsubo cardiomyopathy or the so-called "Broken Heart Syndrome". Signs and symptoms include chest pain, dyspnea, electrocardiographic changes, elevated levels of cardiac troponin I and creatine kinase – MB fraction. This phenomenon was first described in 1991 by Dote et al. who named the syndrome "takotsubo like cardiomyopathy" because the appearance of the heart resembles a pot historically used in Japan to catch octopus (tako in Japanese means octopus; tsubo means pot). The cardiac dysfunction is transient, the left ventricle returns to normal and contractile function is restored within days to weeks. The trigger can be any stressful event: a breakup, the death of a loved one, domestic violence, court appearance, but also some positive events that excite a person excessively like a surprise party.[13] Myocardial dysfunction is thought to occur due to increased myocardial exposure to catecholamines during sympathetic activation. Wittstein et al. monitored that adrenaline, noradrenaline, and dopamine plasma levels were 2-3 times higher in patients with takotsubo cardiomyopathy than in those with classic myocardial infarction.[14] The cardiac apex is particularly sensitive due to the increased distribution of adrenergic receptors.[15] Most patients who have takotsubo cardiomyopathy are postmenopausal women. Perhaps endothelial dysfunction, known to worsen after menopause (because of lowered estrogen levels) further increases vulnerability to sympathetically mediated myocardial stunning.[16] In case of "broken heart syndrome" its own etiology and the added stress of being ill and hospitalized that requires continued psychological support.[13]

Epigenetics

Biology (genetics) defines epigenetics as the study of mitotic or meiotic inherited changes in gene expression or in cellular phenotype. The changes are caused by mechanisms that do not alter the nucleotide order in the DNA molecule as mutations do. Epigenetics deals with hereditary, but also reversible marks that are placed on the unchanged genome, and, therefore, the name of mutations within epigenetics is changed to "epimutation", and, in accordance with genetic terminology, we discuss "epigenome" and "epigenotype".[17] One of the basic epigenetic mechanisms involved in the regulation of gene expression is DNA methylation. DNA methylation is the incorporation of a methyl group into cytosine (mostly in CpG dinucleotide sequences) by DNA methyltransferases and, it most commonly negatively regulates gene expression in gene promoters.[18] Oberlander et al. made the first human study to show an association between prenatal exposure to maternal depressed mood and the methylation status of the promoter and exon 1F of the gene for glucocorticoid receptor (NR3C1) in newborns. The fragment of the NR3C1 gene was analyzed in cord blood mononuclear cells. Exposure to increased third trimester depressed maternal mood is associated with increased neonatal methylation of CpG3site in the fragment of NR3C1. Methylation status of CpG3 in newborns was associated with higher infant stress cortisol reactivity. The association between methylation status of CpG3 and the three month HPA stress response raises the possibility that neonatal methylation at this site might offer an early epigenetic marker of exposure to late gestational maternal depressed mood and risk for altered HPA function in humans. The same glucocorticoid receptor gene was investigated by McGowan et al. who found out that childhood abuse alters HPA stress responses and increases the risk of suicide. They examined epigenetic differences in a neuron-specific glucocorticoid receptor (NR3C1) promoter between postmortem hippocampus obtained from suicide victims with a history of childhood abuse and from suicide victims with no history of childhood abuse. They concluded that hippocampal samples from abused suicide victims showed increased methylation of the exon 1F NR3C1 promoter in comparison with suicide victims with no history of abuse. That is a concrete and tragic evidence of the role of the environment on genetic material.[19]

Cardiology

According to data in 2018, 23048 people died of cardiovascular diseases in Croatia, which is 43.7% of the total number of deaths. In that year, cardiovascular diseases took 49% of the lost lives of women and 38.3% of men.[20] According to the answers on the scale of severity of depressive symptoms collected through The European Health Interview Survey (EHIS) in 2014 and 2015, 10.3% of the Croatian population had mild to moderate depressive symptoms, while 1.2% of the population had moderate to severe depressive symptoms.[21] These statistical data clearly indicate the high incidence of depressive symptoms, depression and cardiovascular diseases in Croatia. It is important to recognize depressive symptoms and to introduce therapy according to the patient's condition. Unfortunately, such patients are often unrecognized in

hospital departments such as those of cardiology and their depressive symptoms are considered as a completely normal reaction to the disease. However, depressive symptoms and unipolar depression significantly affect the further recovery of patients hospitalized due to myocardial infarction. In patients with scores greater than 10 according to the Beck Depression Inventory (BDI), mortality was 17.6% 18 months after infarction while in patients with a BDI score less than 10 mortality was 2.7% (p=0,041). Mortality was 20.0% in patients with unipolar depression and 6.4% in those without a diagnosis of unipolar depression.[22] Lichtman JH et al. as part of the American Heart Association recommend cardiologists and family physicians to screen cardiovascular patients with the risk for depressive symptoms with two questions. Over the past 2 weeks, how often have they been bothered by any of the following problems: First - Little interest or pleasure in doing things, and second - feeling down, depressed, or hopeless? If the answer to both questions is affirmative, then the recommendation is to screen the patient with all PHQ-9 items in order to recognize in time an obstacle for the prognosis of the cardiovascular patient.[23] Epidemiological data should be clarified with pathophysiological relations of depressive symptoms and cardiovascular diseases. Elovanio et al. found that higher levels of depressive symptoms, as indicated by BDI-21, were related to higher levels of CRP. This relationship persisted in men after taking into account a variety of other risk factors such as age, higher glucose, lower HDL, obesity, higher triglyceride level and smoking. In women, obesity was the most evident confounding factor in the relationship between depression and CRP.[24] C reactive protein levels higher than 10 mg/L correlate in a statistically significant manner ($p<0.001$) with a risk higher than 4% to develop a fatal cardiovascular event in the next 10 years.[25] In addition to inflammation, cardiovascular disease is pathophysiologically associated with platelet aggregation. Patients with major depression had a significantly increased activation of the platelet fibrinogen receptor integrin αIIb–β3 complex, the critical final common pathway for platelet activation, compared with healthy controls. Additionally, surface expression of P selectin, a marker of platelet activation, was significantly increased in the depressed patients. Moreover, annexin V protein binding to platelets was also increased. Heightened susceptibility to platelet activation may be a mechanism by which depression is a significant risk factor for cardiovascular disease and mortality after myocardial infarction.[26] Oxidative damage to lipids may also represent a common pathophysiological mechanism by which depressed individuals become more vulnerable to atherosclerosis and its clinical sequelae. Yager et al. revealed that depression is associated with oxidative damage. When comparing values of oxidative stress biomarker 8-iso-prostaglandin F2α, depressed subjects had levels that were 2.34 times higher than controls ($p < 0.001$).[27] Other than depression, we must not neglect other psychosocial variables such as type A behaviour. Among cardiac patients, type A behaviour may lead to minimising both psychological impacts of a life threatening disease and the vulnerability to its consequences, and thus underestimating the need to modify unhealthy lifestyles.[28] Friedman and Rosenman identified six core features of type A behaviour: an intense drive to achieve self-selected, but usually poorly defined goals; competitiveness; a persistent desire for recognition and advancement; involvement in several functions subjected to time restrictions; an accelerated rate of execution of several physical and mental functions and an increased mental and physical alertness.[29] Sirri et al. administered the Structured Clinical Interview for the DSM-IV and the Structured Interview for the Diagnostic Criteria for Psychosomatic Research (DCPR) which identifies 12 clusters, including type A behavior on a sample of 1398 consecutive medical patients (198 with heart transplantation, 153 with a myocardial infarction, 190 with functional gastrointestinal disorders, 104 with cancer, 545 with skin disorders and 208 referred for psychiatric consultation). A cardiac condition was present in 366 out of 1398 patients. There was a significant difference in the prevalence of type A behavior in cardiovascular disease (36.1%) compared with other medical disorders (10.8%).[28] It is necessary to explain in detail to such patients the importance of a proper attitude and right approach to their disease.

Gastroenterology

The London Blitz is an accurate indicator of how stress and fear affect the human body as a whole. Air strikes that began in September 1940 and ended in May 1941 led to an increase in monthly incidences of ulcer perforations by 5.46%. As a control, they used data for periods of 9 months, the same as Blitz lasted, but from January 1937 until the beginning of the bombing.[30] It is also worth mentioning the 1995 Kobe earthquake that killed about 6,000 people and left about 300,000 homeless in just 20 seconds. An earthquake of 7.2 on the Richter scale is an example of a stressful event that has become the subject of numerous studies. In 61 hospitals, a study was conducted the same year and it confirmed that emotional stress increases the risk of complications of peptic ulcer such as perforation or

bleeding. For the control group they used 1994 data. Remarkably, bleeding from 46.8% of gastric and 36.4% of duodenal ulcers was reported in the first two weeks after the earthquake. For comparison with 1994 where the figures for the same period, the same area of Japan and the same ulcers were 10.7% and 2.9%. The authors pointed out that it is recommended to prescribe an antiulcer drug in case of similar natural disasters to those who have a medical history of peptic ulcer.[31] Emotional tension may be accompanied by autonomic system disturbances which produce smooth muscle spasm or hyperperistalsis anywhere in the gastro-intestinal tract. The site of the muscle spasm determines the resultant clinical syndrome. Globus hystericus, painful swallowing, and cardiospasm are esophageal manifestations. Pylorospasm may be an uncomfortable result of stomach localization of smooth muscle spasm. Biliary dyskinesia, fat intolerance, and even clinical jaundice may result from spasm of the gallbladder and biliary tree. Malabsorption of intestinal contents may result from hyperperistalsis. The modification of colon peristalsis can cause diarrhea, and localized smooth muscle spasm of the colon may cause pain or constipation.[32]

Diabetology

The link between diabetes and depression is bidirectional; depression increases the risk of developing type 2 diabetes by 60%,[33,34] and research shows that the prevalence rates of depression are up to three times higher in patients with type 1 diabetes and twice as high in people with type 2 diabetes compared to the general population.[35] It has been shown that chronic activation of the sympathetic nervous system and hypercortisolemia stimulate insulin resistance, visceral obesity and the development of the metabolic syndrome and type 2 diabetes mellitus.[36] Excess cortisol leads to neurogenesis disorders in the hippocampus,[37] a region involved in the development of DM2, but also in the development of depression.[38] Furthermore, chronic stress directly or through the hypothalamic-pituitary-adrenal axis also leads to the dysfunction of the immune system by stimulating the production of pro-inflammatory cytokines such as IL-1, IL-6 and TNF alpha. They act on pancreatic β-cells and cause insulin resistance[39] In addition, it has been shown that an increased number of circulating cytokines is associated with the development of autoimmune diabetes[40] and that they also have a negative effect on the neurotransmitter metabolism, neuroendocrine function, and brain synaptic plasticity[41]. Such changes in the brain may lead to changes in behavior and unhealthy lifestyles such as physical inactivity and consuming an unhealthy diet.[42] There is a problem that arises in treating patients who have been diagnosed with depression and diabetes. Research on the association between antidepressant use and glycemic control has shown that in adults with diabetes, the use of multiple subclasses of anti-depressants significantly increased HbA1C levels, suggesting that treatment of depression may be a risk factor for optimal glycemic control.[43] Previous studies have suggested that short-term antidepressant treatment of non-diabetics with depression has a beneficial effect and improves insulin sensitivity along with improving depression, but in the long run, the effects may be the opposite. Noradrenergic anti-depressants are an exception and may lead to impaired insulin sensitivity even in non-diabetics.[44] Treatment with selective serotonin reuptake inhibitors may improve glycemic control in patients with DM2 depression and is the only class of antidepressants with confirmed beneficial effects on glycemic control in short-term and long-term use.[45] It is important to understand the possible negative effects of anti-depressants on glycemic control and try to keep them to a minimum.

Dermatology

To understand the complex effects of neuro-endocrine responses on stress in skin disorders, it is important to understand that the immune system always responds when stress mediators such as substance P, ACTH and cortisol are released. Receptors for stress mediators can be found on each dermis cell and immune cell that infiltrates the skin. These include innate immunity protagonists such as mast cells, Langerhans cells, neutrophils, and eosinophils, as well as specific adaptive immunity protagonists such as B and T cells.[46,47,48,49] Acute elevated and then rapidly declining cortisol levels lead to the activation of natural killer cells within minutes and the release of proinflammatory cytokines (TNF alpha, IFN gamma) induced by the Th1 response. Although these adaptive responses effectively remove new microbes and tumor cells, they are associated with potential collateral damage, high energy expenditure, and the exacerbation of some diseases such as psoriasis. Unlike acute, chronic stress alters the immune system's response to further stressors. Morning increase in cortisol decreases, and baseline excretion increases during the day as evidence of a change in the hypothalamic-pituitary axis under chronic stress. Persistently elevated levels of endogenous cortisol shift the immune response towards the predominance of Th2 and consequently release of anti-inflammatory

cytokines (IL-4, IL-5) that suppress the initial, predominantly cellular immune response. Activation of the humoral inflammatory response saves energy and avoids collateral damage caused by excessive inflammatory reactions, but at the same time weakens the defenses against new microbes and tumor cells. Furthermore, errors occur in the differences between "foreign" and "own", so that pro-allergenic and autoimmune effects are activated. In addition to a systematic response to stress, there is a local counterpart to it. Namely, keratinocytes, fibroblasts, melanocytes, Merkel cells and endothelial cells producing stress mediators create their own local neuroendocrine system. Interestingly, keratinocytes can not only produce CRH, ACTH, and cortisol but also produce norepinephrine, the neurotrophins NGF and BDNF, as well as a number of other stress mediators such as the neuropeptide SP. At the same time, they have receptors for all of these stress mediators that are important in regulating proliferation and inflammation.[47] Mast cells that are in close contact with sensory nerve fibers play a key role in the excessive immune response to stress. By releasing substance P, these fibers systematically modify the stress response by inhibiting HPA while locally increasing sensory perception, pruritus, and erythema.[50] Both posttraumatic stress and depression correlate with increased pruritus and elevated IgE levels. Interestingly, the neuroendocrine-immune system in depression corresponds to chronic inflammation, especially chronically altered HPA and immune imbalance. Besides depression, the resulting anxiety disorders are the most common mental disorders observed in skin patients, with a prevalence of approximately 20%.[46] Significant psychiatric and psychosocial comorbidity exists in at least 30% of dermatological patients, and untreated comorbid psychiatric disorders adversely affect the efficiency of standard dermatological therapy and the prognosis of mental and physical illness.[51] In general, exacerbation of skin lesions after acute stress occurs within 24 hours. Under psychosocial stress, of physical and psychosocial origin, approximately 50% of patients experience an exacerbation. In psoriasis, stress enhances proinflammatory cytokine release and neurogenic inflammation. In atopic dermatitis, stress exacerbates the Th2 response and neurogenic inflammation, and consequently the severity of the disease. Moreover, exposure to stress in utero or during early development is associated with high levels of IgE, Th2 cytokines, and a higher incidence of symptoms of atopic dermatitis.[46] In view of all these findings, we should pay more attention to reducing stress, as this will reduce both inflammation and the incidence of disease exacerbations.

Alexithymia

Peter Sifneos coined the term alexithymia in 1973 from Greek according to a-deficiency, lexis-word, thymos-emotion.[52] Alexithymia includes the following features: inability to recognize and describe emotions, inability to distinguish feelings and bodily sensations as a result of emotional arousal, narrowed processes of imagination and externally oriented thinking. It can be diagnosed and successfully treated, although it is not included in the International Classification of Diseases.[53] Encouraging the patient to express emotions through behaviors, such as gestures and movements can provide an important source of information that can help them connect with their emotions.[54] In the outpatient general psychiatric population, the prevalence of alexithymia is about 33%, while in the psychiatric hospital population it is 47%. It should be noted that alexithymic depressed patients, regardless of the degree of depression, have more suicidal ideas; more somatic symptoms of distress and they show a significantly lower response to antidepressant therapy (paroxetine) compared to non-alexithymic depressed patients.[55] The leading theory of alexithymia is that a disorder of negative emotion regulation results in altered autonomic, endocrine, and immune activity in alexithymic individuals and thus creates conditions that lead to the development of somatic diseases.[56] Levels of IL-1β, IL-2, IL-4 and Th1 / Th2-lymphocytes (IL-2 / IL-10), CD4-lymphocytes, as well as the ratio of CD4: CD8-lymphocytes, were reduced in women with alexithymia.[57] The identification of risk factors for alexithymia in cancer patients could help improve the quality of life of these patients.[58] Alexithymic patients have shown less progress than non-alexithymic patients during psychotherapy.[59] Recognizing patients with described alexithymic difficulties can help physicians to establish better patient-physician relationships.

Solutions

Finding a proper, individualized therapy for patients with psychosomatic illnesses is a very long process that requires a previously well-conducted medical interview and a comprehensive assessment of the patient's condition and the actual cause of his illness. To achieve this, it is important to ensure sufficient time at the first examination and conversation with the patient. It is also valuable to record key statements in the patient's own words for use in subsequent interviews.[32] Unfortunately, in many hospitals, this is not currently possible because doctors,

due to the overcrowding of the health system, have to conduct a medical interview in 10-15 minutes or less. In order not to omit the assessment of psychosocial factors, it is necessary to educate primary care physicians and specialists. Within the psychodynamic approach in family medicine, Balint groups are useful. Michael and Enid Balint founded Balint's groups to assist family medicine physicians in their daily practical work. Participants in the Balint Group learn to recognize and understand the psychological processes and emotional needs of somatic patients that occur in the treatment of somatic disease, which improves the quality of treatment.[60]

With psychological support and intervention, doctors can teach a psychosomatic patient how to reduce stress. Reducing stress levels leads to better adherence, both in drug treatment and in adopting a healthy lifestyle.[61] The first phase of psychosomatic treatment involves achieving a therapeutic relationship with mutual trust and motivation for treatment. It is necessary to achieve a patient-physician partnership in which physicians and patients make health decisions together and a plan that provides patients with problem-solving skills to improve their self-efficacy.[62] An important step in the healing process is to encourage patients to change bad habits. This proved to be a difficult task in a study described in 2006 in the journal "Patient Education Counseling". Namely, about 75% of patients with cardiovascular disease could not change their bad habits despite the fact that they were informed about risk factors. Patients often deny the link between allostatic load and symptomatology because they are unaware of the delay of symptoms after stressful periods. The worsening of symptoms during the weekend and vacation is a common manifestation of this delay.[63] In addition to effective communication, the psychosomatic approach involves the individualized integration of psychopharmacological and psychotherapeutic procedures. Although antidepressants are effective in treating depression at baseline,[64] their effect on improving medical outcomes has not been demonstrated[65] and often includes side effects, interactions, and an increased likelihood of developing iatrogenic comorbidity.[66] McEwen and Gianaros[67] note that sleeping pills, anxiolytics, and antidepressants are used to suppress the manifestations of allostatic overload, but these agents have side effects and interactions that can be harmful in the long run and sometimes do not result in a solution to the problem they are used for. Therefore, a prudent approach to prescribing psychotropic drugs is needed to ensure a balance between potential benefits and adverse effects. Difficulties in including patients with psychosomatic disorders in psychotherapy are widely recognized. Such patients are often reluctant to participate in psychotherapy and to consider the contribution of psychological factors to their somatic manifestations.[68] To avoid this, it is important to achieve a mutual atmosphere of understanding and trust during the first examination and during the process of diagnosis and treatment. In working with psychosomatic patients, who are an extremely difficult group of patients for psychotherapeutic treatment, it is necessary to eliminate current conflict situations that can significantly affect the psychotherapeutic process. Also, it is very important to prevent the tendency into deeper regression, reduce resistance and "teach" them how to integrate the disease in everyday life, all in an optimally fast time.[53] The psychotherapeutic technique of choice in psychosomatic medicine is supportive psychotherapy which goal is to alleviate and eliminate the difficulties and establish mental balance.[69]

We must not neglect an important study described in 1990 in The Lancet. Ingvard Wilhelmsen et al. were providing cognitive psychotherapy to patients diagnosed with duodenal ulcer in periods without H2 blockers or omeprazole. After 11 months the study was discontinued because 72% of patients who went to psychotherapy had a relapse while in the control group relapses occurred only in 29% of patients. This outcome proved that psychotherapy should not be introduced without pharmacotherapy in the treatment of duodenal ulcers. The therapeutic approach in patients with alexithymia and somatic diseases includes modalities that have the potential to increase awareness of emotions and increase the capacity to regulate and modulate arousal through cognitive processes.[53] Such processes include fantasy, daydreaming, play, verbal communication, and sharing feelings with others. Directing the patient's attention to the expression of emotions through behaviors, such as gestures and movements, can provide an important source of information that can help them connect with feelings.[54] Art therapy, which includes drawing, painting, coloring, and sculpting, has also been proved to be effective in helping people to explore their feelings through creative expression. In this way, patients with alexithymia enter their inner world and build their ability to assess their own feelings, sensations, and perceptions. In his paper published in 1994, Meijer-Degen describes his patient's experience, stating the importance of treatment for her: "For me, art therapy is a way of expressing things that I have never been able to express in conversation alone. Just through conversation, I would never get as far in my healing process as I have now. As a child, I learned to always keep my thoughts and feelings to myself."[70] For

patients who feel uncomfortable talking to others in detail about their traumas and deepest thoughts and feelings, expressive writing could serve. Writing about emotional experiences has been shown to have a positive effect on physical and mental health. James W. Pennebaker[71] summarized the results of several studies of expressive writing in his 1997 scientific paper. Positive effects on immune function have been proven, including T-helper cell growth, antibody response to Epstein-Barr virus, and antibody response to hepatitis B vaccination. Short-term changes in an autonomic activity such as decreased pulse and electrodermal activity have also been observed. McGuire, Greenberg, and Gevirtz (2005) showed that positive effects on autonomic activity can be transmitted in the long term in participants with high blood pressure. One month after expressive writing, those involved in the emotional discovery process showed lower systolic and diastolic blood pressure than before writing. Four months after writing, diastolic blood pressure remained lower than baseline.[72] Meditation is also an extremely important stress management technique, once taught, it can be practiced any time, without special conditions or equipment. Certainly, it is the cheapest method to reduce stress of them all. In 2009, Manocha et al. conducted a large study on 193 general practitioners. It is known that they are the population exposed to great stress, so their response was great. They were given a lecture and workshops with explanations on how to practice meditation and, upon completion, they were given the task to meditate twice a day for the next 2 weeks. The Kessler Psychological Distress Scale questionnaire with 10 questions (K10) was completed by physicians at the beginning of the seminar and at the end of the 2 week home practice session. The mean K10 score before the program was 17.2 (SD: 5.67) and after 2 weeks 14.7 (SD: 3.92). Also, 25.1% of participants from the high-risk category for mild disorder development switched to the low-risk group.[73] In addition to relieving stress, meditation can also be used against pain. Chronic pain, psychosomatic disorder, which affects 20% of the European population and 30% of the US population, is a significant medical and social problem today due to its high prevalence. An indicator of high social burden are pain-related costs that exceed the costs of cancer, heart disease and diabetes combined.[74] An interesting study was conducted on 14 participants in a meditation course center in Tel Aviv. All participants were mentally healthy individuals and they did not suffer from any chronic pain disorder. Their task before and after the meditation course was to rate the intensity of the pain they felt after immersing their hand in icy water on a visual analog scale. Later on, in 7-day intervals, all participants were randomized to receive intravenous naloxone or saline (placebo) before meditation. The results showed that meditating without the use of any medication contributed to a reduction in pain sensation from an average reported 6.11 to 4.21. When naloxone (an opioid antagonist) was administered, the pain they reported was 5.2. These observations support that it was the endogenous opioid system that caused the participants to feel less pain after meditation. All participants had to meet the condition that they had been meditating for at least one year in order to participate. Interestingly there was a positive correlation found between the pain reduction after meditation with years of meditating experience.[75] These studies may be the reason for many physicians to start proposing meditative techniques to patients in their daily practices. Considering all the solutions given, we must emphasize the need for offering personalized solution for each patient. Compassion, the touchstone of good clinical care, involves knowing the person within the patient.[76] Personality can hint at a patient's deeper set of motivations and suggest what aspects of care might be tailored to meet unconscious needs and avoid unconscious threat (e.g., intolerability over a sense of inept care for the narcissist). Personality informed medical approach contours our care delivery using a patient's native personality language. It allows the clinician to translate jargon into a language that patients understand not only linguistically and intellectually but also relationally.[77]

Conclusion

Examples and solutions in our review paper illustrate the strength of the inseparability of mind and body. Mentioning many medical specialties, we can conclude that a psychosomatic approach and given solutions should not be only restricted to psychiatry, medical psychology and psychosomatic medicine, but rather involved into almost any clinical practice. The psychosomatic approach requires a comprehensive personalized assessment that takes into consideration the interaction of the mind, body, and social environment. It is important to educate all clinicians on how emotional burdens can affect health outcomes, and especially family practice physicians who are often the first whom patients ask for help. Psychosomatic approach is the model that we should strive to implement in daily medical practice independently of future technological and pharmacological development.

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