

COMORBIDITY, MULTIMORBIDITY AND PERSONALIZED PSYCHOSOMATIC MEDICINE: EPIGENETICS ROLLING ON THE HORIZON

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SUMMARY

This review focuses first on conceptual chaos and different connotations in psychosomatic medicine, then on new perspectives on comorbidity and multimorbidity, especially from epigenetics perspective. Comorbidity is one of the greatest research and clinical challenges to contemporary psychiatry and psychosomatic medicine. Recently altered gene expression due to epigenetic regulation has been implicated in the development of multifarious mental disorders and somatic diseases. The potential relevance of epigenetics for better understanding and more successful treatment of comorbidity and multimorbidity is described.

Key words: comorbidity - personalized medicine – psychosomatics - epigenetics

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INTRODUCTION

The beginning of the 21st century has brought new hopes of a revolution in medicine based on our advancing knowledge of the mind-body relationship, human genome and comorbidity. Today psychiatry has a historical opportunity to shape the future of health care and medicine in general. The purpose of this paper is to present some new views on interesting and growing family of ideas about comorbidity of mental disorders and somatic diseases and personalized psychosomatic medicine in psychiatry.

PSYCHOSOMATIC MEDICINE: AN OLD FIELD WITH DIFFERENT NAMES AND CONNOTATIONS

Psychosomatic medicine has had different names, definitions and connotations always promoting holistic approach. At the interface of psychiatry and medicine, it has been practiced under multifarious names like psychological medicine, mind-body medicine, cortico-visceral medicine, behavioral medicine, stress medicine, holistic medicine, integrative medicine, consultation-liaison psychiatry, medical-surgery psychiatry, psychiatric care of the complex medically ill and psychosomatics. Psychosomatic medicine is also closely related to many interdisciplinary fields like psychoneuroimmunology, psychoneuroendocrinology, psychocardiology, psychopulmology, psychooncology, psychoreumatology, psychoneuroallergology, and psychodermatology. Psychosomatics can be regarded as: 1. A theory of mind-body relationships 2. A theory of psychosomatic illnesses that can also explain comorbidity of mental disorders and somatic diseases;

and 3. A treatment approach that includes both medical and psychological devices (see also Wolman 1988).

Psychosomatic diseases are defined as a stress-induced physical dysfunctions, like bronchial asthma, hyperventilation syndrome, atrial fibrillation, essential arterial hypertension, functional dyspepsia, irritable bowel syndrome, peptic ulcer, hyperthyroidism, diabetes mellitus, chronic pain, migraine, torticollis, rheumatoid arthritis, atopic dermatitis, chronic urticaria, and pollakiuria (Kubo & Chida 2006). They are also called „psychophysiological disorders“ in which there are demonstrable anatomic and functional changes, and in which psychopathologic processes are considered to be etiologically important (Mai 1976). Mood disorders, anxiety disorders, dissociative disorders, eating disorders, sleep disorders are also stress-related disorders that may cause or be associated with somatic symptoms. In our everyday practice we encounter different group of patients: 1. Patients with comorbid mental and somatic disorders, diseases and illnesses complicating each other's management, 2. Patients with somatoform and functional disorders, 3. Patients with mental disorders that are the direct consequence of a primary somatic disease or its treatment, 4. Patients with somatic disorders that are the direct consequence of a primary mental disorder or its management, 5. Patients with non-explained symptoms (see also Levenson 2007). According to an official definition medically unexplained physical symptoms (MUPS) are physical symptoms for which no relevant organic pathology can be found (Stephenson & Price 2006). In some countries they comprise up to half of visits in primary care as well as up to one third of those in hospital outpatient clinics (Bass & Sharpe 2003).

COMORBIDITY AND MULTIMORBIDITY: AN OLD ENIGMA AND NEW PARADIGM

Community and clinical population studies show that comorbidity is a common phenomenon, the rule rather than the exception. Our current understanding of the multimorbidity and comorbidity of mental disorders and somatic diseases reveals that we have various options as to how to evaluate, explain and describe them. Each option includes its own hypothesis about the etiology and pathogenesis of the phenomenon and determines the appropriate treatment interventions. The method of multiple working hypotheses (see Oschman 2003) consists of „bringing up every rational explanation“ of comorbidity, anticorbidity and multimorbidity phenomena, as well as of „developing every tenable hypothesis“ about them „as impartially as possible“.

The mind-body operating systems and psychosomatic networks in understanding comorbidity and multimorbidity

How many mind-body communication mechanisms exist in human beings is a great puzzle. The multifarious entities comprising the mind-body system and their interactions, taken jointly, constitute a sort of „operating system“ of the human being, which, like the operating system in a computer, works silently in the background, coordinating and regulating all living processes at all levels. These processes involve sensation, movement, the formation and reformation of mind-body structures, consciousness and other mental functions, and physiological functioning, as well as the ways these processes come together in the well-done performance or in good health (see Oschman 2003).

Each person is a unified whole comprised of body, mind and spirit: the genome operates within the context of the cell, the cell within the context of the body, the body within the context of the self, the self within the context of society, and society within the context of the cosmos (Cloninger 2004). The close interconnectedness of the mind, brain, endocrine, and immune systems suggests a unified healing system and self-aware organization. There has been linkage between repressive defenses, chronic helplessness and hopelessness, and dysfunction of the healing system (Dreher 2003).

Several theories are used to explain comorbidity of mental disorders and somatic diseases: *shared predisposition and vulnerability* (personality traits and types, joint genetic abnormalities), *shared risk factors* (stress, psychotrauma, food intolerance, unhealthy life styles, lack of social support, hostile thoughts, negative emotions, pessimism) and *shared mechanisms* (failed or unsuccessful coping, adjustment, resilience or defense mechanisms, endocrine and immune disruption, vital exhaustion, disruption of internal healing system).

Stress as a common factor in disease comorbidity

The role of psychological stress in the development of a wide variety of somatic diseases and mental disorders is well known. Increasing data indicate that stress activates not only hypothalamic-pituitary-adrenal axis, but also inflammatory cytokines and their signaling pathways, like nuclear factor kB (NFkB) both in the periphery and in the brain (see Miller et al. 2008). Stress induced proinflammatory cytokines in the brain significantly reduce the expression of brain-derived neurotrophic factor (BDNF), which play an important role in neuronal growth and development, synaptic plasticity and, ultimately, mental disorders. The epigenetic regulation of the stress response systems like the glucocorticoid receptor gene may be a molecular basis of a specific comorbidity and multimorbidity.

Risk personality types as a common factor in disease comorbidity

Some personality types (A, C, D) may be a common risk factor for multiple somatic disease and mental disorders. Type C characterized with nonexpression of emotions, stoicism, and passive coping style, is a risk factor for cancer and less favourable survival outcome (Dreher 2003). Research in psychoneuroimmunology indicates that personality traits can be associated with deficits of the immune system portions capable for recognizing and eliminating cancer cells. Type D personality is prone to experience negative emotions and to inhibit self-expression in social interactions. Quite a number of studies have indicated type D or „distressed“ personality as being a greater risk for multiple physical (heart disease) and psychological (depression, anxiety) health problems (Dreher 2003, Topić et 2009). If the individual with type D personality cannot reframe hostile cognitions, and find way to creatively express negative emotions (anger, fear, sadness), he or she will be vulnerable to depression and heart disease, which are both breaking points. There is a strong evidence that both heart attack and depression are often preceded by vital exhaustion: extreme fatigue, irritability, and demoralization (see Dreher 2003).

Comorbidity may result from a primary disease

The antecedent model suggests that mental disorder, e.g. depression contributes to the aetiology and progression of somatic illness and this relationship may be mediated by immune, neuroendocrine and inflammatory factors as well as by behavioral factors like smoking, low physical activity, alcohol or drug abuse, diet, etc. (see Steptoe 2007). *The consequence model* suggests mental disorders arising as a result of somatic illness mediated by various direct and indirect biological and behavioral factors and emotional response to diagnosis, treatment and destruction of future life prospects (Steptoe 2007).

„Shared endocrine-disruption“ theory

We are not always victims of our genes, in many cases our genes are our victims. Environmental toxins, including substance abuse, negative interpersonal relationships, social isolation, etc. may be as detrimental as internal, genetically mediated, abnormalities (Nicolescu III & Hulvershorn 2010). A shared endocrine disruption induced by stress, food intolerance, chemicals, etc. may be a common mechanism in comorbidity. Recent evidence indicate that a variety of environmental endocrine disrupting chemicals (EDCs), like bisphenol-A, may be a common factor in multiple diseases including schizophrenia, obesity, heart disease, diabetes, thyroid disease, etc. (Brown 2009, Gruen & Blumberg 2009, Melzer et al. 2010). According to some data, more than 20% of the population in industrialized countries suffers from intolerance or food allergy (Zopf et al. 2009).

Inflammation as a common mechanism in disease comorbidity

Inflammation seems to be a common mechanism in multiple diseases including cardiovascular disease, diabetes, cancer, depression, schizophrenia (see Miller et al. 2009). The activation of innate immune responses (inflammation) may contribute to the development of mental disorders in medically ill individuals as well as to the development of somatic disorders in mentally ill patients.

Human metabolic network topology (MNT) for disease comorbidity

Disease pathophysiology originates from a full or partial breakdown of physiological cellular and mental processes together with subsequent, often compensatory, interactions among components of the genome, proteome, metabolome, and the environment (see Lee et al. 2008). A fundamental question in personalized cellular medicine related to comorbidity is to what degree the topological connectivity of cellular networks is related to the manifestation of human diseases, possibly leading to phenotypic interdependencies. It seems that “connected diseases show higher comorbidity than those that have no metabolic link between them; and the more connected a disease is in the MDN, the higher is its prevalence in population“ (Lee et al. 2008).

Epigenetics of multimorbidity and comorbidity

Epigenetics suggests a novel pathophysiology and entirely new approach to prevention and treatment in the medicine and psychiatry of the 21st century, but the field is still in its infancy. The concept of epigenetic changes has added a new dimension to the study and our understanding of comorbidity and multimorbidity in psychosomatic medicine. There are three basic molecular epigenetic mechanisms: DNA methylation,

histone modification and microRNA dysregulation. DNA methylation, associated with suppression of gene transcription, and histone modification by acetylation, methylation, phosphorylation, and ubiquitylation have a powerful control over the activation or repression of the associated genes (Sweat 2009, Hsieh & Eisch 2010). Histones are small basic proteins which, associate with each other to pack DNA into the nucleus. Histones can be in one of two antagonistic forms, acetylated or deacetylated, and their equilibrium is regulated by the two enzymes, histone acetyltransferases – HAT, and histone deacetylase – HDAC (Zarate et al. 2006). Histone acetylation is associated with increased gene expression, while histones deacetylation results in repressed gene expression. Misregulation and aberrant activities of HAT and HDAC, due to overexpression, mutation, translocation, and amplification, have all been implicated in oncogenesis, the loss of HAT and HDAC regulation has been involved in neuronal dysfunction and degeneration (Zarate et al. 2006). The conserved noncoding microRNAs (miRNAs) function in the cell to regulate gene expression at the posttranscriptional level as part of the RNA-induced silencing complex – RISC (Hebert 2009). Increasing evidence suggests that miRNAs are essential for the development and function of the brain and heart (Hebert 2009). Changes in a single miRNA may have profound effects on hundreds of target genes.

Epigenetic mechanisms play an important role in regulation of gene expression in response to environmental signals, drugs, and experience suggesting that epigenome resides at the interface of the genome and the environment (Sweat 2009). Some common disease like schizophrenia, bipolar disorder, depression, post-traumatic stress disorder, diabetes, cancer, coronary heart disease, etc. may be caused by epigenetic dysregulation of genes when no mutation is present (Handel et al. 2009, Hsieh & Eisch 2010, Handel et al. 2009, Autry & Monteggia 2009, Yehuda et al. 2009, McGowan & Kato 2007). The enormous variation in disease incidence, predisposition, course, outcome as well as in comorbidities and multimorbidities may be due to epigenetic influences from only actual events, but also those that happened many years ago. It seems that aging is accompanied by a substantial shift in epigenetic mechanisms, implying that diseases associated with aging, such as diabetes, coronary heart disease or Parkinson's disease might be related to changes in epigenetic regulatory processes.

Changes in miRNA expression are reported in several diseases, such as cancer, major neurodegenerative disorders including Parkinson's disease, Huntingtonon's disease and Alzheimer's disease, and various heart pathologies including arrhythmia, cardiac fibrosis, angiogenesis, and cardiac hypertrophy (Hebert 2009). The underlying mechanisms of miRNA dysregulation in disease, and specifically in comorbidity and multimorbidity, are not yet clear. Changes in miRNA-regulated pathways may have an important role

in apoptosis, lipid metabolism, and oxidative stress, and may directly or indirectly influence on disease-related genes, such as ACE and APOE. It is “an interesting hypothesis that changes in NFκB and/or YY1 may contribute, at least in part, to abnormal miR-29 expression in both heart and brain” (Hebert 2009). Changes in miRNA expression may have an impact on coexisting neurological, psychiatric and cardiovascular diseases by modulating organ function (brain and heart), accentuating cellular stress, and impinging on neuronal and heart cell survival (see Hebert 2009).

Epigenetic mechanisms are accessible therapeutic targets that are already in development for many diseases, including certain types of cancer, schizophrenia and Huntington's disease (Zarate et al. 2006). Regenerative therapy with stem cells for diabetes, heart failure disease, schizophrenia, dementia, Parkinson's disease, etc. is also a promising new area in epigenetic research.

An example of complementary approach: The role of homocysteine in disease comorbidity

The link between alostatic load, metabolic syndrome, the 1-carbon cycle/folate metabolic pathway, endocrine disruption (e.g. HHA axis dysregulation) and inflammation provides a plausible model for explanation of the comorbidity of mental disorders like post-traumatic stress disorder, major depressive disorder, bipolar disorder and schizophrenia and somatic diseases such as coronary heart disease, cancer, etc. Like cholesterol, homocysteine plays an important role in human health and comorbidity (Jakovljević et al. 2007a,b, Topić et al. 2009). According to some studies, homocysteine levels are up to 40 times more predictive than total serum cholesterol in assessing cardiovascular risk (McLaughlin 2001). HDL cholesterol may protect against hyperhomocysteinemia because it is associated with enzyme paroxonase, that reduces oxidation of homocysteine to the harmful metabolite, homocysteine-thiolactonase (Daly et. 2009). Homocysteine seems to be related to the promotion of lipid peroxidation, interference with platelet aggregation, and fibrin metabolism (McLaughlin 2001). It is interesting that the enhanced secretion of cholesterol and Apo-B from hepatocytes follows elevated levels of homocysteine. Folate deficiency is often associated with higher level of homocysteine, and folate intake can reduce the homocysteine level (Nacci et al. 2008). Folate deficiency aids the incorporation of uracil into the DNA, which can induce DNA instability. Hyperhomocysteinemia may lead to an excessive production of homocysteic acid and cystein sulphinic acid, which act as endogenous agonists of NMDA receptors (Parneti et al. 1997). Homocysteine can damage DNA directly via the generation of reactive oxygen species (Nacci et al. 2008). Chronic hyperhomocysteinemia may have an impact on cellular methylation involving DNA, RNA,

various proteins and phospholipids (see McLaughlin 2001). Elevated homocysteine levels have been reported to be linked to altered DNA repair, chronic fatigue syndrome, rheumatoid arthritis, diabetes, cancer (colorectal, uterine cervical, laryngeal), inflammatory bowel disease, gastric atrophy, depression, Alzheimer's disease, Parkinson's disease, and chronic alcoholism (Bleich et al. 2004, Bottiglieri 2005, Sachdev 2005, Folstein et al. 2007). S-adenosylmethionine (SAM) is useful in the treatment of depressive disorders, either as an adjunct to standard antidepressants or even as a single agent as well as in prevention and treatment of heart diseases. Omega-3 fatty acids, vitamins B6 and B12 and folates are safe and effective dietary supplementation strategy in patients with depression, schizophrenia, bipolar disorder as well as in patients with heart disease.

COMORBIDITY AND PERSONALIZED PSYCHOSOMATIC MEDICINE IN PRACTICE

Comorbidity is an extremely important issue in personalized medicine for medication choice, medication tapering, prediction and avoidance of unwanted side-effects, follow-up treatment and achieving full recovery (Jakovljević et al. 1993, 2006 Jakovljević 2009). In patients with comorbidity mental disorder may 1. modify subjective reactions to somatic symptoms (amplification or), 2. reduce motivation to care for somatic illness (demoralization), 3. lead to maladaptive direct physiological effects on bodily symptoms, and 4. reduce the ability to cope with somatic illness through limitation of energy, cognitive capacity, affect regulation, perception of shame or social stigma. On the other side, somatic comorbidity in psychiatric patients is associated with 1. shortened life-time because the mortality due to somatic diseases is higher in patients with major mental disorders than in general population (Maj 2009), 2. more and severe adverse events during psychopharmacotherapy, 3. more treatment noncompliance and nonadherence, 4. lower quality of life and lower subjective and objective well-being in general. The development of an appropriate integration between mental health and somatic health care is a crucial issue in psychiatry and psychosomatic medicine.

The development of personalized molecular medicine is a laudable goal, but there are multiple barriers to its implementation (Dean 2009). It is important to note that the concept of personalized psychosomatic medicine is extending beyond pharmacogenetics and pharmacogenomics, particularly contemporary treatment algorithms and it includes the consideration of all scientific information valid for diagnosis and successful treatment of multiple diseases. Each patient is a unique individual in health and diseases who should get highly specific and personally adjusted treatment for her or his comorbidities and multimorbidities including mental health protection and promotion.

The history of psychiatric genetics is mainly a story of unreplicated discoveries and disappointed expectations, however epigenetics offers a new hope to personalize psychosomatic medicine. Challenges for personalized psychosomatic medicine will include the technology of individual whole-genome sequencing and the concept that the phenotype reflects a complex interaction of genes and the environment. Genetic and biomarker testing now on the horizon could improve objective assessment of disease, disease comorbidity, disease severity and monitoring of treatment response.

CONCLUSION

Epigenetics holds substantial promise for better understanding previously intractable conundrums in psychosomatic medicine. Epigenetic mechanisms might be important in etiology for many complex diseases, like coronary disease, diabetes mellitus, cancer, multiple sclerosis, chronic obstructive pulmonary disease, juvenile idiopathic arthritis, major depressive disorder, bipolar disorder, schizophrenia and many others. Although current knowledge of the epigenetic basis of disease and treatment is very limited, epigenetic mechanisms are already accessible therapeutic targets that are in development for many mental disorders and somatic diseases.

REFERENCES

1. Anisman H, Merali Z & Hayley S: Neurotransmitter, peptide and cytokine processes in relation to depressive disorder: Comorbidity between depression and neurodegenerative disorders. *Progress in Neurobiology* 2008; 85:1-74.
2. Autry AE & Monteggia LM: Epigenetics in suicide and depression. *Biological Psychiatry* 2009; 66:812-813.
3. Bass C & Sharpe M: Medically unexplained symptoms in patients' attending medical outpatient clinics. In Weatherall DA, Ledingham JG & Warrell DA (eds): *Oxford Textbook of Medicine*, 4th edition, 1296-1303. Oxford University Press, 2003.
4. Bleich S, Degner D, Sperling W, Bonsch D, Thurauf N & Kornhuber J: Homocysteine as a neurotoxin in chronic alcoholism. *Progress In Neuro-Psychopharmacology & Biological Psychiatry* 2004; 28:453-464.
5. Bottiglieri T: Homocysteine and folate metabolism in depression. *Progress In Neuro-Psychopharmacology & Biological Psychiatry* 2004; 29:1103-1112.
6. Brown JS Jr.: Effects of bisphenol-A and other endocrine disruptors compared with abnormalities of schizophrenia: An endocrine-disruption theory of schizophrenia. *Schizophrenia Bulletin* 2009; 35:256-278.
7. Daly C, Fitzgerald AP, O'Callaghan P, Collins P, Cooney MT, Graham IM, on behalf of the COMAC group: Homocysteine increases the risk associated with hyperlipidemia. *European Journal of Cardiovascular Prevention & Rehabilitation* 2009; 16:150-155.
8. Cloninger CR: *Feeling Good: The Science of Well-Being*. Oxford University Press, 2004.
9. Dean CE: Personalized medicine: Boon or budget-buster? *The Annals of Pharmacotherapy* 2009; 43:958-962.
10. De Leon J: The future (or lack of future) of personalized prescription in psychiatry. *Pharmacological Research* 2009; 59:81-89.
11. Dreher H: *Mind-Body Unity – A New Vision for Mind-Body Science and Medicine*. The Johns Hopkins University Press, Baltimore & London, 2003.
12. Folstein M, Liu T, Peter I, Buel J, Arsenault L, Scott T & Qiu WW: The homocysteine hypothesis of depression. *Am J Psychiatry* 2007; 164:861-867.
13. Gilbody S, Lewis S & Lightfoot T: Methylene tetrahydrofolate reductase (MTHFR) genetic polymorphisms and psychiatric disorders: A HuGE Review. *American Journal of Epidemiology* 2006, doi:10.1093/aje/kwj347.
14. Gruen F & Blumberg B: Endocrine disruptors as obesogens. *Molecular and Cellular Endocrinology* 2009; 304:19-29.
15. Handel AE, Ebers GC & Ramagopalan SV: Epigenetics: molecular mechanisms and implications for disease. *Trends in Molecular Medicine* 2009; 16:7-16, doi:10.1016/j.molmed.2009.11.003
16. Hebert SS: Putative role of microRNA-regulated pathways in comorbid neurological and cardiovascular disorders. *Cardiovascular Psychiatry and Neurology* 2009; article ID 849519, 5 pages. doi:10.1155/2009/849519.
17. Hsieh J & Eisch AJ: Epigenetics, hippocampal neurogenesis, and neuropsychiatric disorders: Unraveling the genome to understand the mind. *Neurobiology of Disease* (2010), doi:10.1016/j.nbd.1010.01.008
18. Jakovljević M, Mueck-Šeler D, Jelovac N, Ercegović N, Plavšić V, Čulig V, Koršić M & Montani M: Gastrointestinal ulcer disease in schizophrenia and major depression: Platelet serotonin and plasma cortisol investigation. *Psychiatria Danubina* 1993; 5:277-294.
19. Jakovljević M, Šarić M, Nađ S, Topić R & Vuksan-Čusa B: Metabolic syndrome, somatic and psychiatric comorbidity in war veterans with post-traumatic stress disorder. *Psychiat Danub* 2006; 18:169-176.
20. Jakovljević M, Crnčević Ž, Ljubičić Đ, Babić D, Topić R & Šarić M: Mental disorders and metabolic syndrome: A fatamorgana or warning reality? *Psychiatria Danubina* 2007; 19:68-75.(a)
21. Jakovljević M, Reiner Ž & Miličić D: Mental disorders, treatment response, mortality and serum cholesterol: A new holistic look at old data. *Psychiatria Danubina* 2007; 19:270-281.(b)
22. Jakovljević M: Integrating brave new psychiatry of the person, for the person, by the person and with the person: The postmodern turn. *Psychiatria Danubina* 2008; 20:2-5.
23. Jakovljević M: Transdisciplinary holistic integrative psychiatry – A wishful thinking or reality? *Psychiatria Danubina* 2008b; 20:341-348.
24. Jakovljević M: The side-effects of psychopharmacotherapy – Conceptual, explanatory, ethical and moral issues: Creative psychopharmacology instead of toxic psychiatry. *Psychiatria Danubina* 2009; 21:86-90.
25. Kubo C & Chida Y: Psychoneuroimmunology of the mind and body. *International Congress Series* 2006; 1287:5-11.
26. Lee DS, Park J, Kay KA, Christakis NA, Oltvai ZN & Barabasi AL: The implications of human metabolic network topology for disease comorbidity. *PNAS* 2008; 105:9880-9885. www.pnas.org/cgi/doi/10.1073/pnas.0802208105

27. Levenson JL: *Essentials of Psychosomatic Medicine*. American Psychiatric Publishing, Inc., Washington, DC, 2007.
28. Mai F: Management of „psychosomatic“ problems in clinical practice. *CMA Journal* 1976; 114:684-686.
29. Maj M: Physical health care in persons with severe mental illness: a public health and ethical priority. *World Psychiatry* 2009; 8:1-2.
30. McLaughlin KJ: The role of homocysteine in human health. *Journal of Orthomolecular Medicine* 2001; 16:33-39.
31. Melzer D, Rice NE, Lewis C, Henley WE & Galloway TS: Association of urinary bisphenol A concentration with heart disease: Evidence from NHANES 2003/06. *PLoS ONE* 2010; 5:1-9. www.plosone.org
32. Miller AH, Sonia Ancoli-Israel, Bower JE, Capuron L & Irwin MR: Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol* 2008; 26:971-982.
33. Nacci A, Dallan J, Bruschini L, Traino AC, Panicucci E, Bruschini P, Mancini V, Rognini F & Fattori B: Plasma homocysteine, folate, and vitamin B12 levels in patients with laryngeal cancer. *Arch Otorinolaryngol Head Neck Surg* 2008; 134:1328-1333.
34. Niculescu III AB & Hulvershorn LA: Toward early, personalized, rational polypharmacy in psychiatry: a tri-dimensional approach. *Psychopharm Review* 2010; 45:9-16.
35. Oschman J: *Energetic Medicine in Therapeutics and Human Performance*. Butterworth – Heinemann, Elsevier Science (USA), 2003.
36. Stephenson DT & Price JR: Medically unexplained physical symptoms in emergency medicine. *Emerg Med J* 2006; 23:595-600. doi: 10.1136/emj.2005.032854
37. Perneti L, Bottiglieri T & Lowenthal D: Role of homocysteine in age-related vascular and non-vascular diseases. *Aging* 1997; 9:241-257.
38. Reser JE: Schizophrenia and phenotypic plasticity: Schizophrenia may represent a predictive, adaptive response to severe environmental adversity that allows both bioenergetic thrift and a defensive behavioral strategy. *Medical Hypotheses* 2007; 69:383-394. doi:10.1016/j.mehy.2006.12.031
39. Sachdev PS: Homocysteine and brain atrophy. *Progress In Neuro-Psychopharmacology & Biological Psychiatry* 2005; 29:1152-1161.
40. Steptoe A: Integrating clinical with biobehavioural studies of depression and physical illness. In Steptoe A (ed): *Depression and Physical Illness*, 397-408. Cambridge University Press, 2007.
41. Sweat JD: Experience-dependent epigenetic modifications into the central nervous system. *Biol Psychiatry* 2009; 65:191-197.
42. Šagud M, Mihaljević-Peleš A, Pivac N, Jakovljević M & Mueck-Šeler D: Lipid levels in female patients with affective disorders. *Psychiatry Res* 2009; 168:218-21.
43. Topić R, Markelić I, Vuksan-Čusa B, Marčinko D, Čima A, Aukst-Margetić B & Jakovljević M: Homocysteine and Cholesterol Serum Levels and Types A/B and D Personality in Psychiatric Patients: A Complex and Controversial Issue. *American Psychiatric Associations Annual Meeting* 16-21.5.2009
44. Wolman BB: *Psychosomatic Disorders*. Plenum Medical Book Company, New York & London, 1988.
45. Yehuda R & Bierer LM: The relevance of epigenetics to PTSD: Implications for the DSM-V. *Journal of Traumatic Stress* 2009; 22:427-434.
46. Zarate CA, Singh J & Manji HK: Cellular plasticity cascades: Targets for the development of novel therapeutics for bipolar disorder. *Biol Psychiatry* 2006; 59:1006-1020.
47. Zopf Y, Baenkler HW, Sibermann A, Hahn EG & Raithe M: The differential diagnosis of food intolerance. *Deutsches Arzteblatt International* 2009; 106:359-370. Doi:10.3238/arztebl.2009.0359

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