

PSYCHOPHARMACOTHERAPY AND COMORBIDITY: CONCEPTUAL AND EPISTEMIOLOGICAL ISSUES, DILEMMAS AND CONTROVERSIES

Miro Jakovljević

University Department of Psychiatry, Clinical Hospital Centre Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia

SUMMARY

Comorbidity is one of the greatest research and clinical challenges to contemporary psychiatry. Mental disorders are often comorbidly expressed, both among themselves and with various sorts of somatic diseases and illnesses. Shifting the paradigm from vertical/mono-morbid interventions to comorbidity and multimorbidity approaches enhances effectiveness and efficiency of human resources utilization. Comorbidity studies have been expected to be an impetus to research on the validity of current diagnostic systems as well as on establishing more effective and efficient treatment including personalized pharmacotherapy.

Key words: *comorbidity – multimorbidity - integrative medicine - personalized psychopharmacotherapy*

* * * * *

INTRODUCTION

The fact that some mental disorders and some somatic diseases occur together more frequently (comorbidity) or rarely (anticomorbidity) than it would be expected by chance is very intriguing (Jakovljević et al. 1993). There are many reasons why comorbidity is an important issue, not only in the context of psychopathology and diagnostic classification, overlapping clinical manifestations and pathogenesis, primary and secondary processes, spectrum disorders concept and systematic diseases concept, but also in the context of rational and creative psychopharmacotherapy, patient's self-management and health care utilisation, and

drug development strategy. With regards to the global burden of disease and high demands on healthcare systems attributable to comorbidity, there is an urgent need for better understanding the coexistence of mental disorders and somatic diseases in order to develop more effective and efficient prevention and treatment strategy with improvement of the well-being, functioning and quality of life of psychiatric patients.

Although there is a considerable literature on comorbidity between mental disorders and somatic diseases, this topic is strongly associated with a lot of conceptual, epistemiological and treatment challenges, dilemmas and controversies.

Table 1. Some controversies regarding the meaning of the term comorbidity (Krueger & Markon 2006)

- Comorbidity is the coexistence of two or more diseases, pathological conditions or „clinical entities“ in the same patient (Feinstein 1970)
- Any clinically relevant phenomenon separate from the primary disease of interest that occurs while the patient is suffering from the primary disease, even if this secondary phenomenon does not qualify as a disease per se (Feinstein 1970)
- The joint occurrence of two or more mental disorders occurring with each other, and/or with medical conditions (Klerman 1990)
- A reasonable label for co-occurring entities that may not rise to the conceptual level of bona fide categories with clear cut etiologies and pathophysiologies, not only in psychiatry, but in whole medicine (Spitzer 1994)
- The presence of an antecedent or concurrent psychiatric syndrome in addition to the principal diagnosis (Strakowski 1995)
- Two or more diseases with distinct aetiopathogenesis (or if the aetiology is unknown, with distinct pathophysiology or organ and system), that are present in the same individual in a defined period of time (Vella et al. 2000)
- The association of two distinct diseases in the same individual at a rate higher than expected by chance (Bonavita & de Simone 2008)
- The co-occurrence of a real disease (a medical pathology clearly defined and with distinct boundaries) with a distinct clinical entity (Aragona 2009)

Table 2. Dilemmas and controversies

- Does comorbidity means the co-occurrence of two or more necessarily separate, distinct and aetiologically unrelated diseases or may include aetiologically related pathological conditions (spectrum disorders concept)?
- Do life-time comorbidity, intra-episode comorbidity and comorbidity within family represent different comorbidity categories/types or different dimensions of the same unitary phenomenon?
- Do personality disorders classified in DSM Axis II represent subclinical/attenuated forms or developmental phase of DSM Axis I psychopathology or DSM Axis I independent comorbid conditions?
- Does dimensional approach underestimate comorbidity rates and reduce multiple diagnoses to a single diagnosis through the use of hierarchical conventions (hypocomorbidity)? Does categorical approach overestimate comorbidity rates encouraging multiple diagnoses (hypercomorbidity)? Dimensional-Categorical approach gap and hypocomorbidity – hypercomorbidity dilemma
- Does comorbidity have a real and stable structure or the structure of comorbidity is artefactual?
 - The fact that various mental disorders are rarely present in isolation manner could be viewed as an evidence that comorbidity is an artifact of current diagnostic systems imposing categorical distinctions not existing in reality (Maj 2005)
 - An increased comorbidity of mental disorders with somatic illnesses has been claimed to be misclassification due to an overlap of symptoms or the medical consequence or the cause of the mental disorder (Weissman 2006).

The distinction between real or true and artefactual or false comorbidity is not an easy task. According to some authors „the artefactual comorbidity is mostly the consequence of the DSM/ICD convention to 'split' diagnostic entities into numerous specific narrowly-defined disorders rather than 'lump' them together into a few broadly-defined categories (First 2005, May 2005, Aragona 2009). Comorbidity, syndromal complexity, double or multiple diagnosis involves complex and various philosophical and epistemological issues.

COMORBIDITIES ARE INDIFFERENT TO PROFESSIONAL SPECIALTIES: INTEGRATIVE MEDICINE IS AN IMPERATIVE IN PRACTICE

The simultaneous presence of multiple pathological conditions in the form of comorbidity and multimorbidity is more a rule than an exception in all populations of patients (Starfield 2006). It may be useful to make a distinction between comorbidity and multimorbidity. Most patients with chronic illnesses do not have a single, predominant condition (Grumbach 2003). Rather, many of them have multimorbidity, the simultaneous presence of multiple chronic illnesses. The term comorbidity should be related to co-existence of two or more pathological conditions when one is predominant.

Mental disorders of all types are more common in patients with somatic illness compared with the general population, and to turn around, somatic illnesses of all sorts are more common in

psychiatric patients than in general population. Patients with comorbid mental disorders and somatic diseases experience a lot of difficulties in adequate health care. Psychiatrists often fail to recognize and treat somatic disease in their patients, similarly as specialists in other medical disciplines often do not recognize mental disorders in their patients and not provide appropriate treatment for them.

With regard to the resolutions of medical and psychiatric comorbidity and multimorbidity, various disciplines are involved like psychosomatic medicine, liaison psychiatry, behavioral medicine, mind-body medicine, biopsychosocial medicine, integrative medicine, complementary medicine, integrative psychiatry and health psychology. The existence of the specialty of liaison psychiatry is an unwise message: despite having medical diploma, only a few among psychiatrists are sufficiently well-trained in medicine to be able to deal with patients who have a mental and a somatic disease in the same time (Sartorius 2007). The creation of the specialty of psychosomatic medicine has a similar message in the contradiction. The primary objective for psychosomatic medicine psychiatrists is the improvement of psychiatric care of patients with complex medical conditions who are encountered in general and chronic care hospitals, offices of primary care or specialist physicians and in many other health care environments (Gitlin et al. 2004). The issue of comorbidity and multimorbidity highlights the intricacy of integrative medicine and integrative psychiatry and the complexity of providing holistic care.

The conceptual basis of comorbidity rests on theories about interconnections of mind, brain and body, health and disease, wellness and illness (see Jakovljević 2007, 2008b). The brain is very important for functioning of the mind and body. According to some authors „the most important factor in why a person becomes ill lies in the brain“ (Vitetta et al. 2005). Mind also impacts the brain and body as well as the body always impacts the brain and mind. The state of human mind, that associates psychosocial factors with emotional states such as depression and with behavioral dispositions which include hostility and psychosocial lifestyle stresses, can directly and significantly influence human physiology and health outcomes (Vitetta et al. 2005). The human body is more than just a physical organism or functioning machine that fluctuates between health and illness. It is also the focus of very different beliefs about its social and psychological significance, its structure and its function (Helman 2007). The body image and illness/disease perceptions, which includes all the ways that an individual conceptualizes and experiences her or his body and illness/disease, consciously or unconsciously, is acquired as a part of growing up in particular family, culture and society. The mind-

body dualism that dominated in medicine and psychiatry for a long time has been transformed to a more holistic and integrated conceptualization of disease and health (Jakovljević 2008b). Its basic view is that mind, brain and body interact and influence each other in health and illness such that comorbidity represents the result of complex interactions and processes. The development of the science of psychoneuroimmunoendocrinology provides an enormous possibilities to understand the pathogenesis of comorbidity between mental disorders and somatic diseases including the role of the mind and stress in the causes of diseases. Increased inflammatory responses, in part related to impaired regulation by the neuroendocrine system, interact with pathophysiologic pathways known to be involved in the regulation of mood and behavior, and thus may mediate the development of mental disorders in patients with somatic diseases. This increasing appreciation of the role of inflammation in behavioral pathology and mental disorders is complementary to an increasing awareness of inflammation as a common mechanism in multiple diseases including cardiovascular disease, diabetes and cancer (Miller et al. 2008).

Table 3. Interpretative approach to the phenomena of comorbidity

Somatic disease-Mental disorder Comorbidity

- Mental disorders with preexisting somatic diseases: The development of comorbid mental disorder that occurs in relation with a somatic disease might be the result of the distress attributable to the disease or it may be secondary to psychosocial stress associated with it (Anisman et al. 2008).
Somatic disease predisposes to the development of mental disorder
Somatic disease causes mental disorder (organic or symptomatic mental disorders)
Mental disorder is a reaction to somatic disease (adjustment disorders, reactive mental disorders)
- Somatic diseases with preexisting mental disorder
Mental disorder predisposes to the development of somatic disease
Somatic diseases caused by the psychopharmacotherapy – iatrogenic comorbidity
Mental disorder causes somatic disease
- Shared determinants model: *Somatic disease and mental disorder are induced or caused by the same predisposing or casual factor („pathogenetic interplay“ with overlapping signs and symptoms)*
Given that inflammatory factors might influence both mental disorders and somatic diseases cytokines may contribute to the high degree of comorbidity (see Anisman et al. 2008)

Comorbidity of two or more mental disorders

- One mental disorder predisposes another one (predisposing pathogenesis)
 - One mental disorder is the developmental phase of the another one (generalized anxiety disorder progresses to depression – the helplessness-hopelessness theory)
 - Two or more mental disorders with overlapping pathogenesis (spectrum disorders concept)
 - Mixed states (schizoaffective disorder, anxiety-depressive disorder) or comorbid states (comorbidity of schizophrenia and bipolar disorder, comorbidity of anxiety and depression)
-

The relationships between mental disorders, somatic illnesses, biological, psychological and behavioral processes may be understood as a synchronicity as well as causal chains. Comorbidity and syndromal complexity are widely prevalent among patients with mental disorders as well as among somatic patients. There are several models trying to explain these relationships. *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 the 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). *The shared determinants or common pathogenesis model* suggests common biological mediators, psychosocial adversity, psychological traits, emotional distress, and behavioral factors like smoking, low physical activity, alcohol and drug abuse, bad diet etc. which lead to both mental disorder and somatic disease (Steptoe 2007). According to *a single diathesis model*, a genetic constellation and/or an early insult, predisposes the patient to a series of later pathological conditions, so a mental disorder and a somatic illness may appear after life stress or alostatic overload as conditions expressing the diathesis. Diathesis refers to predisposition to disease/illness including constitutional, biological factors as well as psychological variables such as cognitive and interpersonal susceptibilities (Ingram & Price 2001). «Invulnerability», «resistance to disorder», «competence», «protective abilities», and «resilience» are terms indicating various degrees of opposite to vulnerability. At the most extreme vulnerability end of the continuum range, a small life stress is enough to result in a disorder whereas at the resilient end of the continuum range a great deal of stress will be necessary before disorder develops (Ingram & Price 2001). In other words, with enough distress even the most resilient people will be at significant risk to develop a mental disorder, although these symptoms will probably be milder than those of a vulnerable individual who experiences low to moderate stress,

and will almost certainly be milder than those of the vulnerable individual under significant distress (Ingram & Price 2001).

THE CRISIS OF THE CURRENT CLASSIFICATION: COMORBIDITY AND SEARCH FOR NEW POSSIBLE DIAGNOSTIC PHENOTYPES

Contemporary psychiatry is in crisis. It seems that our comorbidity concepts are inadequate for understanding all complexity of this phenomenon and for the time being we are in an impasse. The term comorbidity has different connotations and these different connotations have become the source of controversies and conflicts. The explosion of comorbidity rates led the DSM and ICD toward a scientific crisis (Aragona 2009). The essence of scientific progress is an emergence of a paradigm shift that produces the significant restructuring of the ways in which the scientific field defines its problems (Kuhn 1970, Klerman 1990). The cognitive component of paradigm shift refers to the theories, hypotheses, and ideas by which scientific field is delineated, and the rules used to conduct research and evaluate evidence (Klerman 1990). The communal component refers to the collectivity of scientists who share the ideas and values and acknowledge the validity of a particular form of scientific „truth“ (Klerman 1990). Comorbidity puzzle solving will probably bring with itself new scientific paradigms and perspectives with new diagnostic phenotypes and refining the old ones.

Most disease are the consequence of the breakdown of cellular processes, but the relationships among genetic/epigenetic defects, the molecular interaction networks underlying them, and the disease phenotypes are still poorly understood (Lee et al. 2008). Human diseases can be grouped into a human disease network based on the genes the diseases share as well as on the shared metabolites and correlated metabolic reactions (Lee et al. 2008). A fundamental question with regard to comorbidity issue is to what degree the topological connectivity of cellular networks is related to the manifestation of human diseases, possibly leading to phenotypic interdependencies. The impact of disease-inducing gene mutations is often not limited to the products of the mutated gene but may spread and affect the activity of other cellular components, causing apparently unrelated disease phenotypes and resulting in comorbidity.

Given the unknown environmental, lifestyle, and treatment related factors that all contribute to comorbidity, it is not a priori evident if the metabolic network-based dependencies are strong enough to manifest themselves at the individual and population level (Lee et al. 2008). It seems that the systematic mapping of metabolism-based links between disease may help us uncover some critical disease comorbidities and multimorbidities and explain their shared pathophysiology.

Genetic/family studies of mental disorders have usually ignored somatic diseases which may aggregate with the disorder of interest in patients and/or families. Attempts for finding possible new phenotypes on the basis of life-time comorbidity using epidemiological and clinical observation, represent a new interesting research paradigm. Some studies suggest that some genes on chromosome 13 influence susceptibility to a pleiotropic syndrome that includes panic disorder, bladder problems (interstitial cystitis), severe headaches/migraine, mitral valve prolapse and thyroid problems (Weissman 2006). The lifetime prevalence of panic disorder seems to be significantly, more than fourfold, higher among patients with interstitial cystitis compared with control subjects. First-degree relatives of patients with interstitial cystitis compared with control subjects are significantly more likely to have panic disorder, thyroid disorder, urological problem and complete syndrome (Weissman 2006). Irritable bowel syndrome, chronic fatigue syndrome, celiac disease, and fibromyalgia may also be a part of the syndrome (see Weissman 2006). It seems that pleiotropy does not require that all elements of the expression of the phenotype be present in an individual. Interstitial cystitis is supposed to be a local manifestation of a systemic disease, possibly an autoimmune disorder, but this is controversial.

COMORBIDITY ON THE DOORSTEPS OF PERSONALIZED MEDICINE AND PSYCHOPHARMACOTHERAPY

Comorbidity is an extremely important issue in a comprehensive, individual and personalized patient management as well as in a rational and creative psychopharmacotherapy (see Jakovljević 2009). Given the fact that comorbidity between mental disorders and somatic diseases is fairly common, it is logic that the presence of a mental disorder may hinder alleviation of symptoms of a

somatic disease as well as the presence of a somatic disease may hinder remission of a mental disorder. In addition, due to possible adverse effects medication for one pathological condition may aggravate or induce another pathological condition. Comorbidity is frequently followed by patient's negative illness perceptions. Negative illness perceptions are associated with poorer recovery, adherence to treatment and increased healthcare use independently of objective parameters of illness severity (Petrie & Weinman 2006). In patients with comorbidity mental disorder may 1. modify subjective reactions to somatic symptoms, 2. reduce motivation to care for somatic illness, 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 contemporary medicine and psychiatry.

Medicine, as well as psychiatry, is in the process of a paradigm shift. Instead of relatively broad pathological diagnoses, population-based risk assessments, and nonspecific „one-size-fits-all“ therapies, we are moving to an individualized and personalized medicine. The concept of personalized medicine is based on hypothesis that each patient is unique human being with unique genotype and phenotype, personal and family history, life story and script, one or more comorbid diseases, specific nutritional habits and specific preferences in medication taking not always in concordance with recommended ones. Personalized medicine offers highly specific and individually adjusted treatment for a concrete patient in given circumstances. Personalized psychopharmacotherapy pursues trends in personalized medicine. In addition to the influence of genetic, personal and environmental elements, it also encompasses the influence of comorbidity on

pharmacodynamics and pharmacokinetics of mental health medications as well as on possible drug interactions. The issue of comorbidity highlights the intricacy of the whole person approach, or person-centered medicine (Jakovljević 2008a) rather than each component diseases approach.

Comorbidity is an extremely important issue in personalized medication choice, medication tapering, prediction and avoidance of unwanted side-effects, follow-up treatment and achieving full recovery. Comorbidity is a multi-interpretable

phenomenon and can be explained from different theoretical and conceptual perspectives. Clinical complexity of comorbidity and multimorbidity should be appraised, understood and formulated through different perspectives in order to get crucial clinical tools such as a reliable diagnostic model and an effective, personalized and holistic treatment (see table 4). Each perspective has a different internal logic, specific and distinct, but equally plausible interpretation as well as different useful treatment implications (Jakovljević 2008).

Table 4. Comorbidity from different perspectives

Perspective	Explanation
Medical/Disease	Disease concept works in psychiatry just as it does in somatic medicine. This perspective focuses on identifying symptoms of different diseases, linking symptoms to specific pathophysiological process involved, and prescribing specific treatment. Comorbidity is associated with two or more different pathophysiological processes, which may be or not etiologically related (etiological, interactional and coincidental types). The assumption that disease captures the essence of illness is erroneous (disease without illness, and illness without disease).
Dimensional	This perspective shifts from the biological determinism to the appreciation of meaning in human behavior in health and illness. From this perspective, comorbidity may be derived from personal dispositions (diathesis) and stressful life circumstances (stress-diathesis model). Personality weakness and risky traits have been shown to account directly for comorbidity patterns. Treatment is focused on helping patients to use personality resources and strenghts to increase their well-being and decrease the risks of comorbidity.
Cognitive conflicting	Pathological behavior leading to comorbidity may be related to cognitive strategies, misinterpretations and misrepresentations. Much of comorbidity and multimorbidity may be created by errors or biases in thinking because our thoughts are important determinants of our actions. When wrong, negative, self-limiting and self-defeating thoughts are corrected, health can be established again.
Behavioral	Some comorbidity may be associated with patient's behavior, not directly to previous disease (so called behavioral comorbidity). Some risky/unhealthy behaviors are caused by diseases so onset of another comorbid disease may be the consequence of such behaviour. Some other unhealthy behaviors are related to combination of physiological need, conditioned learning, and choices. In such cases comorbidity may result from what patients are doing wrong.
Narrative	From this perspective, comorbidity may be related to the patient's specific life story and experience, self-attitude, or particular unconscious intentions (life-script). The outcome of the same disease may be very different within different life scripts.
Systemic	Mental disorders and somatic diseases/illnesses can be conceptualized within different body, energy, mental, social and etc. systems. Comorbidity may reflect the problems in different, more or less related systems The treatement addresses promotion of the healthier structural relationships and interactions within the system and between different systems.
Spiritual	Spiritual beliefs are of great importance to many patients and may have a significant impact on comorbidity. Trust in providence which is love and wisdom, belief in great power which is the source of reassurance and hope, ability to find meaning in suffering and illness, gratitude for life which is perceived as a gift, ability to forgive have protective and promotive effects on health.

At each particular case of comorbidity in each phase of the treatment, the psychiatrist needs to select the primary perspective that best fits the patient and then integrate the other complementary

perspectives into the formulation of comprehensive treatment. Treatment programme should be multimodal, pluralistic, multiperspective, integrating, holistic and comprehensive, always addressing

specific needs of patients (person centered psychiatry). Well-being therapy, life coaching and healthy life-style package including nutritional advice and exercise is of the great importance for achieving full recovery from comorbidity, better life-satisfaction, happiness and well-being by patients.

CONCLUSION

Better understanding of the comorbidity between mental disorders and somatic diseases/illnesses is closely associated with better understanding of the complex interrelationships between physiological and psychological processes in the context of „mind-body connection“, and help us more frequently to achieve successful treatment and effective prevention. Shifting the paradigm from vertical and monomorbidity interventions to comorbidity and multimorbidity approach facilitates the association between the successful treatment of mental disorders with the successful treatment for comorbid somatic disease, and vice versa.

REFERENCES

1. Anisman H, Merali Z & Hayley S: Neurotransmitter, peptidic and cytokine processes in relation to depressive disorder: Comorbidity between depression and neurodegenerative disorders. *Progress in Neurobiology* 2008; 85:1-74.
2. Aragona M: The role of comorbidity in the crisis of the current psychiatric classification system. *Philosophy, Psychiatry & Psychology* 2009; 16:1-11.
3. Aragona M: About and beyond comorbidity: Does the crisis of the DSM bring on a radical rethinking of descriptive psychopathology? *Philosophy, Psychiatry & Psychology* 2009; 16:29-33.
4. Blashfield RK: Comorbidity and classification. In Maser JD & Cloninger CR (eds): *Comorbidity of Mood and Anxiety Disorders*, 61-82. American Psychiatric Press, Inc., 1990.
5. Bonavita V & De Simone R: Towards a definition of comorbidity in the light of clinical complexity. *Neurol Sci* 2008; 29:s99-s102.
6. First MB: Mutually exclusive versus co-occurring diagnostic categories: The challenge of diagnostic comorbidity. *Psychopathology* 2005; 38:206-210.
7. Frances A, Widiger T & Fyer MR: The influence of classification methods on comorbidity. In Maser JD & Cloninger CR (eds): *Comorbidity of Mood and Anxiety Disorders*, 41-59. American Psychiatric Press, Inc., 1990.
8. Gitlin DF, Levenson JL & Lyketsos CG: Psychosomatic medicine: A new psychiatric subspecialty. *Academic psychiatry* 2004; 28:4-11.
9. Grumbach K: Chronic illness, comorbidities, and the need for medical generalism. *Annals of Family Medicine* 2003; 1:4-7.
10. Helman CG: *Culture, Health and Illness*. Hodder & Arnold, London, 2007.
11. 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.
12. Jakovljević M: The brave new psychiatry: A pluralistic integrating transdisciplinary approach in theory and practice. *Psychiatria Danubina* 2007; 19:262-269.
13. Jakovljević M: Integrating brave new psychiatry of the person, for the person, by the person and with the person: The postmodern turn. *Psychiatria Danubina* 2008a; 20:2-5.
14. Jakovljević M: Transdisciplinary holistic integrative psychiatry – A wishful thinking or reality? *Psychiatria Danubina* 2008b; 20:341-348.
15. 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.
16. Klerman GL: Approaches to the phenomena of comorbidity. In Maser JD & Cloninger CR (eds): *Comorbidity of Mood and Anxiety Disorders*, 13-37. American Psychiatric Press, Inc., 1990.
17. Krueger RE & Markon KE: Reinterpreting comorbidity: A model based approach to understanding and classifying psychopathology. *Annu. Rev. Clin. Psychol.* 2006; 2:111-33.
18. 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
19. Kuhn TS: *The Structure of Scientific Revolutions*, 2nd Edition. International Encyclopedia of Unified Science. Vol. 2, No 2. University of Chicago Press, Chicago, 1970.
20. Maj M: 'Psychiatric comorbidity': An artefact of current diagnostic systems? *Brit J Psychiatry* 2005; 186:182-184.
21. Maj M: Physical health care in persons with severe mental illness: a public health and ethical priority. *World Psychiatry* 2009; 8:1-2.
22. Miller AH, Ancoli-Israel S, Bower JE, Capuron L & Irwin MR: Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol* 2008; 26:971-982.

23. Petrie KJ & Weinman J: *Why illness perceptions matter. Clinical Medicine* 2006; 6:536-539.
24. Sartorius N: *Physical illness in people with mental disorders. World Psychiatry* 2007;6:2-3.
25. 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.*
26. Starfield B: *Threads and yarns: Weaving the tapestry of comorbidity. Annals of Family Medicine* 2006; 4:101-103.
27. Strakowski SM, Keck PE Jr, McElroy SL, Lonzak HS & West SA: *Chronology of comorbid and principal syndromes in first-episode psychosis. Compr Psychiatry* 1995; 36:106-112.
28. Vella G, Aragona M & Aliani D: *The complexity of psychiatric comorbidity: A conceptual and methodological discussion. Psychopathology* 2000; 33:25-30.
29. Vitetta L, Anton B, Cortizo F & Sali A: *Mind-body medicine – Stress and its impact on overall health and longevity. Ann. N.Y. Acad. Sci.* 2005; 492-505. doi: 10.1196/annals.1322.038
30. Weissman MM: *Epidemiological phenotype hunting – Panic disorder and interstitial cystitis. In Eaton WW (ed): Medical and psychiatric comorbidity over the course of life. American Psychiatric Publishing, Inc., Washington, DC, 2006.*

Correspondence:

Prof. dr. Miro Jakovljević, MD, PhD
University Psychiatric Clinic Rebro, Clinical Hospital Centre Zagreb
Kišpatićeva 12, 10000 Zagreb, Croatia
E-mail: predstojnik_psi@kbc-zagreb.hr