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Comorbidity as an epistemological challenge to modern psychiatry

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In spite of a considerable progress in comorbidity research and huge literature on it, this phenomenon is one of the greatest epistemological, research and clinical challenges to contemporary psychiatry and medicine. Mental disorders are very often comorbidly expressed, both among themselves and with various sorts of somatic diseases and illnesses. Therefore, 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 within the frame of person centered transdisciplinary psychiatry and integrative medicine. This review focuses first on conceptual chaos and different connotations, then on transdisciplinary perspectives of comorbidity and multimorbidity. The authors compiled an extensive set of various views and perspectives, dilemmas and controversies, in order to evaluate what we know and what we don't about comorbidity, what comorbidity is and what comorbidity is not, what are facts and what are non-facts on comorbidity and multimorbidity.

Keywords: comorbidity, multimorbidity, epistemology, false diagnosis, transdisciplinary integrative psychiatry

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INTRODUCTION

Over the last several decades we have witnessed a steady accrual of a substantive body of knowledge in comorbidity medicine. However, paraphrasing P.D. Scott, comorbidity can be considered as the rock on which many fine theories are wrecked and upon which better ones can be built. It is a paramount epistemological challenge to contemporary psychiatry as well as to medicine in general. This challenge includes quite a number of conceptual and explanatory questions and dilemmas. *Epistemology* is a branch of philosophy which deals with knowledge, including the nature of knowledge itself, how it is obtained, what we know, and how we know what we (think we) know as well as how knowledge relates to concepts such as truth and belief. *Nomotetic knowledge* is defined by a tendency to generalization including the efforts to derive laws that explain objective phenomena. It comes from the study of groups which represent populations, normally using quantitative methodologies. On the opposite, *idiographic knowledge* is based on the tendency to specify including efforts to understand the meaning of contingent, accidental and often subjective phenomena. It is derived from the study of individuals and properties which set them apart from other individuals, normally using qualitative methodologies (Slade 2011). With regards to comorbidity epistemology raises both conceptual and explanatory questions in nosotropic and etiotropic framework. *Conceptual questions* are related to the various definitions and meanings of terms like disorder, disease, illness, sickness, rival disease, comorbidity, real comorbidity and pseudocomorbidity, anticomorbidity, trans-syndromal and trans-nosological comorbidity, multimorbidity, polymorbidity and polipathy, hypercomorbidity and hypocomorbidity, systemic disorders/diseases, complex disorders, circle or spectrum disorders , multifactorial diseases, co-occurring, co-existing, concomitant, cluster and comorbid disorders, dual diagnosis, etc. (see Jakovljević 2009). *Explanatory questions* are relevant to mechanisms underlying comorbidity and multimorbidity related to mind-body operating systems and psychosomatic networks, human metabolic network topology, shared endocrine-disruption, inflammation and immune dysfunctions, epigenetic mechanisms, etc. (see

Jakovljević et al. 2010). Mental disorders are multifactorial, multidimensional and etiologically complex and that is why explanatory models should refer mostly to explanatory pluralism rather than to biological reductionism. Furthermore, we are still waiting for explanations of causes, types and structure of causal or etiological and random or epiphenomenal comorbidity, active and passive comorbidity, symmetric and asymmetric comorbidity, one disease pervasive and equal diseases comorbidity, life-time and intra-episodic comorbidity, etc.

As the comorbidity issue has been studied extensively in the past decades, it is timely to reconsider the state of art and science in comorbidity field from the epistemological perspective. This review focuses first on conceptual chaos and different connotations in comorbid medicine, then on some new perspectives on comorbidity and multimorbidity in psychiatry and mind-body medicine.

UNDERSTANDING COMORBIDITY: A TERM WITH DIFFERENT MEANINGS

It seems that our comorbidity and multimorbidity concepts are inadequate for understanding all complexity of these phenomena and for the time being we are in an impasse. The terms comorbidity and multimorbidity referring to simultaneous existence or sequential appearance of two or more physical and/or psychological (mental) disorders in the same patient have different meanings and connotations which have become the source of controversies and conflicts. As there is no consensus with regards terminology, the use of imprecise language reflecting "the conceptual cacophony in psychiatry" (Kecmanović 2011b) is usually associated with imprecise thinking and corresponding confusion in comorbidity field, hence it may be useful to review different definitions of comorbidity (see table 1).

In general the term comorbidity has three

Table 1. Definitions of Comorbidity (see Krueger and Markon 2006)

-The coexistence of two or more diseases, pathological conditions or "clinical entities" in the same patients. 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 itself as a disease per se (Feinstein 1970)
- General tendency toward co-occurrence, so that the presence of any disorder increases the odds of having almost any other disorder (Boyd and Burke 1984)
-The joint occurrence of two or more mental disorders arising each other, and/or with medical conditions (Klerman 1990)
- The presence of more than one specific disease in a person in a specific period of time (Burke 1990)
-The presence of any additional coexisting ailment in a person with a particular index disease (Heninger 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 the whole medicine (Spitzer 1994)
-The concurrent presence of independent disorders (van Praag 1993).
-The presence of an antecedent or concurrent psychiatric syndrome in addition to the principal diagnosis (Strakowski 1995)
- Two or more diseases with distinct etiopathogenesis (or if the etiology 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)
-When investigators look at multimorbidity in relation to the main condition under study they should use the term comorbidity (Fortin et al. 2005)
-The co-occurrence of two diagnoses at the same time for a single patient independently of etiological and /or pathway considerations (Banaschewski et al. 2007, Rothenberger et al. 2010).
- The association of two distinct diseases in the same individual at a rate higher than expected by chance (Bonavita and 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 2009b).
- The co- occurrence of mental and physical disorders in the same person, regardless of the chronological order in which they occurred or the causal pathway linking them (Felker et. al. 1996, van den Akker et al. 1998, Valderas et al. 2009)
-"Co-morbidity" is a term which might be better employed to refer to patients whose physical illness is accompanied by a mental disorder (Goldberg 2011)

meanings: 1. two or more medical conditions existing simultaneously but independently of each other; 2. two or more medical conditions existing simultaneously and interdependently of each other what means that one medical condition causes, is caused, or is otherwise related to another condition in the same individual; 3. two or more medical conditions regardless the causality. Some authors define comorbidity as the simultaneous presence of two or more diseases in some individual which are associated with each other through pathogenetic mechanisms in contrast to multimorbidity which refers to the simultaneous presence of two or more diseases not having any connection to each other through pathogenetic mechanisms. According to Grumbach (2003) the term comorbidity should be related to the co-existence of two or more pathological conditions when one is predominant. With regards to the Kuhnian model of inevitable and accidental side of diagnostic system or concept (see Aragona 2009b), comorbidity could also refer to diseases which occur together more frequently than it would be expected by chance (the inevitable side), while multimorbidity refers to diseases which appear together randomly or not more commonly than it would be expected by chance (the accidental side). There is also an interesting possibility to use the term comorbidity for the co- occurrence of two or more diseases, the term hypercomorbidity for the association of two or more diseases at a higher rate than expected by chance, and the term hypocomorbidity instead of the term anticomorbidity for diseases that appear together at a lower rate than expected. The central roadblock to progress in comorbidity field is the missing of a cohesive, multidimensional, integrated model that incorporates the known facts of the comorbidity phenomena. There have been no clear rules for the formulation of clinical diagnosis for comorbid phenomena distinguishing the primary and background diseases as well as their complications and accompanying pathologies, or secondary diseases. Hence, the need for this small comorbidity dictionary (see table 2).

From table 2 it is clear how we face a labyrinth full of different terms and possible relationships between multiple and simultaneous disorders in the same person. Many different words like multimorbidity, polymorbidity, multifactorial diseases, multidimensional diseases, polypathy, multisystem diseases, dual diagnosis, pluralpathology etc. are used as synonyms of comorbidity. It is difficult, frequently impossible to distinguish subtypes of comorbidity seen in table 2 unless patogenesis of the disorders is well understood and explained. With regards to the concept of primary and secondary disease, distinction can be made on the basis of chronological sequence, causal inference ("due to"), symptomatic predominance and disease severity.

WHAT WE KNOW AND WHAT WE DON'T KNOW ABOUT COMORBIDITY

In clinical practice comorbidity is underrecognized, underdiagnosed, underestimated and undertreated so that we can speak about comorbidity anosognosia. Due to terminological and conceptual confusion, from an epistemological perspective it is time to consider what we know (table 3) and what we don't know (table 4) about comorbidity, what comorbidity is and what comorbidity is not, what are facts and what are meta-facts about comorbidity.

The essence of scientific progress is an emergence of a paradigm shift producing a significant restructuring in the definitions the scientific field gives to 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 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; this process will naturally lead to a re-definition of the old diagnostic phenotypes. In this paper we compiled an extensive set of facts and meta-facts in order to understand the nature of comorbidity and multimorbidity in psychiatry and mind-body medicine. We have various options regarding how to evaluate, explain and describe simultaneous existence or sequential appearance of additional one or more mental or/

Table 2. Some useful definitions for the formulation of clinical diagnosis in case of comorbidity/polymorbidity

Arbitrary comorbidity: initial alogism of the combination of disease is not proven, but soon can be explained from clinical and scientific points of view (see Wikipedia 2012).
Associating disease: nosological item not connected etiologically and pathogenetically with the primary disease.
Background disease: disease which helps in the occurrence or adverse development of the primary disease, increases its dangers and helps in the development of complications. As well as the primary disease, it requires immediate treatment, e.g. type 2 diabetes (see Wikipedia 2012).
Causal comorbidity: describes disease clustering with a pathophysiological relation between the different diseases, e.g. shared risk factors (see Schaefer et al. 2010).
Cluster comorbidity: indicates statistically significant associations between diseases without a causal explanation (see Schaefer et al. 2010).
Complex genetic disorders: there is not a one-to-one correspondence between gene and disease (Potash 2006)
Complicated comorbidity: the result of the primary disease and often subsequent after some time (see Wikipedia 2012).
Complicating comorbidity: illustrates the case when one disease is caused by another disease and cannot be explained without its precursor (see Schaefer et al. 2010).
Complications: nosologic items which have pathogenic relation to the primary disease, supporting the adverse progression of the disorder, causing acute exacerbation - a part of the complicated comorbidity (see Wikipedia 2012).
Concordant comorbidity: diseases as parts of the same pathophysiologic risk profile and more likely to share the same management and are more likely to be the focus of the same disease management plan, e.g. type 2 diabetes mellitus and hypertension (see Valderas et al., 2009)
Concurrent comorbidity: defines the random coexistence of diseases (Schaefer et al. 2010).
Conjugated disease: the complication of the primary disease related to its etiological and pathogenetic factors (the cause of comorbidity).
Diagnostic comorbidity: an associated disease whose manifestations can simulate those of the index disease, e.g. pneumonia and pulmonary infarction (see Valderas et al., 2009). "Diagnostic comorbidity is likely whenever diagnostic criteria are based on patterns of symptoms that are individually nonspecific" (Maser and Cloninger 1990).
Discordant comorbidity: diseases that are not directly related in either pathogenesis or management and do not share an underlying predisposing factor (e.g. type 2 diabetes mellitus and irritable bowel syndrome)
Double diagnosis: when two diagnoses are made independently and in isolation from each other (Lavori 1990)
Dual diagnosis: simultaneous occurrence of two or more kinds of mental illnesses, of which one concern the problematic abuse of psychoactive substance (WHO 1995, UN 2000, see Sawicka et al. 2009)
Etiological comorbidity: caused by concurrent damage to different organs and systems, which is caused by a singular pathological agent (e.g. due to chronic alcoholism, pathologies associated with smoking, systematic damage due to collagenoses) – (see Wikipedia 2012).
General propensity to ill health: the possibility of an etiological overlap between various disorders (see Neeleman et al. 2001)
Heterotypic comorbidity: disorders from different diagnostic groupings, e.g. major depression and conduct disorder (see Valderas et al., 2009)
Homotypic comorbidity: disorders within a diagnostic grouping, e.g. major depression and dysthymia (see Valderas et al., 2009).
Iatrogenic comorbidity: a result of the negative effect of a treatment. Mental health medications certainly contribute to somatic comorbidity in individuals with mental disorders as well as somatic medications may induce mental disorders (see Wikipedia 2012).
Mental multimorbidity: the coexistence of two or more mental disorders in the same patients (Axis I and II comorbidity)
Multisystem disease: a disease that usually affects a number of psychophysiologic systems, organs and tissues during its course
Non-organic comorbidity: when it cannot be established that an organic factor initiated and maintained the comorbid disturbance (Samet et al. 2004)
Non-specified (NOS) comorbidity: the presence of singular pathogenetic mechanisms of development of diseases (see Wikipedia 2012).
Organic comorbidity: when an organic factor initiated and maintained the comorbid disturbance (Samet et al. 2004)
Polipathy:diseases with different etiologies and pathogenesis, each of which separately could not cause death, but concurring during development and reciprocally exacerbating each other, they cause the patient's death (e.g. fracture of the surgical neck of the femur due to orthostatic hypotension and hypostatic pneumonia in a patient treated with levomepromazine) – (see Wikipedia 2012).
Primary disease: disease which is the cause of seeking medical help or the reason for patient's death. In the case of several primary diseases it is important to understand the combined primary diseases, rival or concomitant (see Wikipedia 2012, Samet et al. 2004). Primary disorder is independent of subsequent secondary disorder (Feighner et al., 1972).
Prognostic comorbidity: diseases (in relation to an index disease) graded according to their anticipated effects on therapy and life expectancy (see Valderas et al., 2009). Disorders predisposing an individual to develop other disorders and complications have prognostic comorbidity (Maser and Cloninger 1990).
Rival disease: the concurrent nosological item interdependent in etiology and pathogenesis, but equally sharing the criterion of a primary disease (see Wikipedia 2012).
Secondary disease: disease that follows and result from an earlier disease, injury, or event.
Somatic multimorbidity: the coexistence of two or more somatic diseases, pathological conditions or "clinical entities" in the same patients. Triads of the six most prevalent individual chronic conditions (arterial hypertension, lipid metabolism disorders, diabetes mellitus, chronic ischemic heart disease, chronic low back pain, osteoarthritis) correspond to the multimorbidity spectrum of almost half of the multimorbid sample (van den Busche et al. 2011)
Trans-nosological comorbidity: coexistence of two or more nosological units pathogenetically related to each other (see Wikipedia 2012).
Trans-syndromal comorbidity: coexistence of two or more syndromes pathogenetically related to each other (see Wikipedia 2012).

and somatic disorders. Each option includes its own hypothesis about the etiology and pathogenesis of the phenomenon, specific terminology and determines the appropriate treatment interventions. The method of multiple working hypotheses (Oschman 2003) consists of "bringing up every rational explanation" of comorbidity, anticomorbidity and multimorbidity phenomena as well as of "developing every tenable hypothesis" about them "as impartially as possible".

The distinction between real or true and artifactual or false comorbidity is not an easy task. According to some authors the artifactual comorbidity in psychiatry is mostly a 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, Maj 2005, Aragona 2009b). Future comorbidity research should be associated with new scientific paradigms and perspectives, as well as with new diagnostic phenotypes and refinement of the old ones.

Table 3. Facts about comorbidity/multimorbidity

1. For time being comorbidity and multimorbidity are usually synonyms referring either to the co-occurrence or co-existence of two or more necessarily separated, distincted and aetiologically unrelated diseases as well as to aetiologically related pathological conditions (spectrum disorders). It seems plausible to differentiate these two terms.
2. The simultaneous presence of multiple pathological conditions in the form of comorbidity and multimorbidity is more a rule but rather an exception in all populations of patients (see also Starfield 2006).
3. Multimorbidity appears in an almost infinite number of variants with a mostly low prevalence.
4. High comorbidity or multimorbidity rate is associated with the high prevalence of mental disorders and chronic somatic diseases/illnesses.
5. The relations between mental disorders and somatic diseases are self-perpetuating and mutually reinforcing.
6. Having one type of disorder/illness is a risk factor for developing the other. Patients meeting criteria for any given personality disorder are quite likely to meet criteria for two or more (see Frances et al. 1990).
7. High comorbidity rate is associated with increasing longevity, but multimorbidity is not just a condition of old age. With regards to mental disorders, about 80% of children and 45% of adults develop at least one comorbid condition (Cramer et al. 2010, Rothenberger et al. 2010).
8. The pathways leading to comorbidity are complex and usually bidirectional or circular. They include sequential processing networks leading to specific pathologies and disorders/diseases associated with those specific pathologies as well as parallel processing networks that are interconnected, exchange and spread maladaptive information and beliefs.
9. Comorbidity may significantly change across time.
10. Exposure to early trauma and chronic stress may be a risk factor for both mental and somatic disorders and their comorbidity.
11. Increased vulnerability or decreased resilience may be a risk factor for both mental and somatic disorders and their comorbidity.
12. Perinatal complications, personality features like neuroticism, impulsivity, pessimism, etc., perceived lack of parental care, oxidative stress, mitochondrial energy metabolism dysregulation, metabolic disorders, disrupted circadian rhythms etc. may contribute to comorbidity and multimorbidity.
13. Unhealthy life styles may be risk factors for both mental and somatic disorders and their comorbidity.

Table 4. What we don't know about comorbidity/multimorbidity

1. What precisely causes the comorbid physical, cognitive, emotional and behavioral dysfunctions? When do these dysfunctions set in? Why are they manifested in the way they are? How do they evolve?
2. How to make appropriate differentiations between comorbidity, multi or polymorbidity, systems diseases, spectrum disorders, complex (genetic) disorders, primary and secondary disorders?
3. Do life-time comorbidity, intra-episode comorbidity and comorbidity within family represent different comorbidity categories/types or different dimensions of the same unitary phenomenon?
4. Do personality disorders classified in DSM Axis II represent subclinical/attenuated forms and/or developmental phases of DSM Axis I psychopathology or, on the opposite, are DSM Axis I disorders independent comorbid conditions?
5. Does the 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)?
6. Does comorbidity have a real and stable structure? Or else is the structure of comorbidity variable?
7. Why sicker patients are more likely to meet criteria for multiple psychiatric diagnoses suggesting multiple mental disorders to be more comorbid with one another?
8. How frequently reported comorbidity is an artifact of current diagnostic systems imposing categorical distinctions not existing in reality?
9. How to distinguish pathogenic from pathoplastic factors in comorbidity?

COMORBIDITY AND MULTIMORBIDITY: MULTIDIMENSIONAL AND MULTI-INTERPRETABLE PHENOMENA

Comorbidity is a multi-interpretable phenomenon and can be explained from various, but mutually complementary, theoretical and conceptual perspectives. Multilevel modeling of comorbidity includes explanatory variables at different levels, focusing on cases where level 1 parameters nest into level 2 parameters. 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 5). Each perspective has a different internal logic, which is specific and distinct, that leads in another way to equally plausible interpretation as well as different useful treatment implications (Jakovljević 2008b, 2009).

With regards to the resolutions of medical and psychiatric comorbidity and multimorbidity, various disciplines are involved like, for example 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 the psychiatrits are sufficiently well-trained in medicine to be able to deal with patients who having mental and somatic diseases at the same time (Sartorius 2007). The creation of the specialty of psychosomatic medicine has a similar message in the counterdirection. The primary objective for the 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 understanding and care.

A multisystem disease usually affects a number of systems, organs and tissues during its course. Mental disorders of all types are more common in patients with somatic illness compared with the general population, and to turn around, somatic disorders/illnesses of all sorts are more common in psychiatric patients than in the general population. Therefore, it can be said that mental disorders are characterized by high rates of somatic comorbidity as well as by very high rates of metabolic, oxidative stress and pro-inflammatory risk factors. This suggests that major mental disorders are multisystem diseases. The question here is how to define what is comorbidity and what is a multisystem disorder in psychiatry. Do depression, diabetes and coronary heart disease represent comorbid disorders or a multisystem or complex mind-body disease?

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

Diagnostic classification in psychiatry allows psychiatrists and other mental health workers to communicate effectively and it is reliable as any in medicine. However, the validity issue whether disorders are real diseases reflecting specific pathology or pathophysiology remains highly problematic (Sirgiovanni 2009, Zorumski 2010). Many diagnostic categories are indistinctive without clear demarcation between them. Due to multifarious nosological problems in psychiatry and mental health counseling the term comorbidity refers frequently to the presence of two or more diagnoses rather than real disorders or diseases. In line with that view clinical and epidemiological studies have indicated high rate of co-occurrence between DSM diagnoses (Narrow 2011). In general this is legitimate, e.g. a patient with schizophrenia and substance abuse, but in many cases multiple diagnoses reflect lack of syndromic and systemic thinking as well as a failure to use parsimonious logic and a longitudinal perspective for describing the illness course (Zorumski 2010).

Illusory comorbidity: An artifact of the ICD-10 and DSM-IV-TR diagnostic systems

The cause of comorbidity is a puzzle, which may be related to the very conceptualization

of what a mental disorder is (Aragona 2009b,c, Borsboom et al. 2011). The very concept of mental comorbidity is problematic and its application to individual patients is difficult (Meehl 2011). The phenomenon of psychiatric comorbidity indicates that psychiatric classification systems are not optimal yet. If comorbidity is the rule rather than the exception then the classification system loses plausibility and practicability (Feger 2001). According to van Praag (1993) comorbidity is the parasite of nosological classifications in psychiatry. The fact that various mental disorders are rarely present in isolation manner could be considered as an evidence that comorbidity is an artifact of current diagnostic systems imposing categorical distinctions not existing in reality (Maj 2005, Cramer et al. 2010). An increased comorbidity of mental disorders with somatic illnesses has also been claimed to be misclassification due to an overlap of symptoms, the medical

Table 5. 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 the symptoms to a 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 and personality assessment in health and illness. Considering this perspective, comorbidity may be derived from personal dispositions (diathesis) and stressful life circumstances (stress-diathesis model). Personality weakness (vulnerability), risky traits and low resilience have been shown to account directly for comorbidity patterns. Treatment is focused on helping patients to use personality resources and strengths to increase their well-being and decrease the risk of comorbidity
Cognitive	Pathological behavior leading to comorbidity may be related to conflicting cognitive strategies, misinterpretations and misrepresentations. Much of comorbidity and multimorbidity may be created either 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 the patient's behavior, not directly to previous disease (so called behavioral comorbidity). Some risky/unhealthy behaviors are caused by diseases so that the onset of another comorbid disease may be a consequence of such behavior. Some other unhealthy behaviors are related to combination of physiological need, conditioned learning, and bad choices. In such cases comorbidity may result from what patients are doing wrong. Comorbidity may be the consequence of coincidental reinforcement of different behaviors, regardless of genetic predisposition
Narrative	This perspective emphasizes the importance of life experience, personality organization and psychological script for understanding the individual psychopathology. The psychological script contains the ongoing program for the person's life drama and tendencies to some mental disorders. From the narrative viewpoint, comorbidity may be related to the patient's specific life story and experience, self-attitude, specific behavior or particular unconscious intentions (life-script)
Systemic	Mental disorders and somatic diseases/illnesses can be conceptualized within different body, energy, mental, social systems, etc. Comorbidity may reflect the problems in different – more or less – related systems. Therefore there are many roads to comorbidity and which one will be taken depends on dysfunctioning psychophysiologic systems and mind-body networks
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 a 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

consequence or the cause of the mental disorder (Weissman 2006).

Illusory comorbidity may be a by-product of ICD-10 and DSM-IV-TR diagnostic systems related to the: 1: proliferation of diagnostic categories in recent classifications based on explicit operative atheoretical criteria; 2. rule that the same symptom could not appear in more than one disorder; 3. lack of hierarchical ordering of symptoms (Maj 2005); 4. use of polythetic criteria with quantitative diagnostic thresholds lacking hierarchical distinctions among symptoms (Aragona 2009a). The number of diagnoses has grown from about 100 disorders in DSM-I in the 1950s to about 270 disorders in DSM-III in 1980 to nearly 300 disorders and about 500 diagnoses in the current version of DSM-IV (see Zorumski 2010). Mental disorders based on atheoretical phenomenal description differ from diseases and illnesses which are defined on the knowledge of its etiology and/or pathophysiology (Aragona 2009a). This atheoretical definition of mental disorders may also have contributed to the current co-occurrence of multiple psychiatric diagnoses to be higher than in the past. Polithetic definitions are based on a list of characteristics all of which possessed by some units of the diagnostic category, but not by all units of the class (Aragona 2009a,b). That is why polithetic diagnostic criteria linked to the lack of hierarchical distinctions among psychiatric symptoms may be associated with an increased rate of co-occurrence between DSM diagnoses.

According to Maj (2005) the phenomenon of comorbidity is strongly related to the nature of psychopathology. The nature of psychopathology is intrinsically composite and changeable, so that co-occurrence of multiple disorders could be better reformulated as the complexity of many psychiatric conditions. From the psychodynamic point of view, the interaction of congenital predisposition, individual experiences and the type and success of defense mechanisms employed may generate an infinite variety of combinations of symptoms and signs. According to the psychobiological viewpoint, the noxious stimuli perturb a variety of neuronal circuits. The extent to which the various neuronal circuits will be involved varies individually, and consequently psychiatric conditions will lack symptomatic consistency and predictability (van Praag 1993). From the evolutionary viewpoint mental disorders are the expression of preformed response patterns shared by all humans, which may be activated simultaneously or successively in the same individual by noxae of different nature.

Scientific crisis in psychiatric nosology: The Churning Continues

Comorbidity had become so rampant in psychiatry that the explosion of comorbidity rates led the DSM and ICD toward a scientific crisis (Aragona 2009c, Sirgiovanni 2009) and opened Pandora's box with questioning whether psychiatric disorders were real and true scientifically proved diseases or rather items of a political agreement. According to Jaspers 'true diseases' are those with clear boundaries among themselves and with normality while 'circles' (schizophrenia, manic depressive insanity) have clear boundaries with normality, but not among themselves. Current psychiatric disorders have porous and fuzzy boundaries, they broadly overlap and there is no strict border between mental disorders and normalcy. Instances of systematic or non-random co-occurrence of DSM-IV or ICD-10 disorders may reflect shared risk factors for the development of mental disorders, or could represent different manifestations of the same underlying disorder. Furthermore, if two disorders share similar symptoms like anxiety and mood disorders (apprehensive feelings, worry, upset, distress, tension, irritability, helplessness, pounding heart, shortness of breath, sweating) than an increased co-occurrence is quite expected. The implications for reconsidering diagnostic classification are quite clear: generalized anxiety disorder and depressive disorders should belong to the same category of affective disorders. On the axis I major depressive disorder (MDD) and generalized anxiety disorder (GAD) are not only strongly comorbid one another, but with a wide range of other psychiatric disorders. A mechanistic approach to psychiatric classification cannot provide a systematic reformulation of psychiatric taxonomy (Sirgiovanni 2009) contributing to the clarification of numerous comorbidity and multimorbidity issues.

Nosology in medicine and psychiatry refers

to the study of the classification of disorders, diseases and illnesses. Well-operationalized diagnostic categories should provide a basis for agreement and reliability across observers as well as for treatment guidelines. The appropriate nosology is associated with an understanding of the clinical constellation of symptoms in the context of knowledge of the underlying etiology and pathophysiology. How can we know whether we have a proper nosology? We can say to have a proper classification system when our diagnostic categories are able to guide the prognosis, treatment and prevention of the named disorder/disease/illness entities. Diagnostic structure in psychiatry is still based on categorical classifications with less attention to dimensional aspects of psychopathology, which ultimately may diminish diagnostic reliability (Narrow 2011). The term 'dimensional' refers to three different meanings in the context of psychiatric classification: 1. a group of correlated symptoms called dimensional symptoms; 2. the occurrence and distribution of subclinical "dimensional symptoms" in the general population; 3. the appreciation of meaning in human behavior and personality assessment in health and illness evaluation (Regier 2007, Dutta et al. 2007, Jakovljević 2009). Variation in expression of the mental disorders can be better understood in terms of quantitative differences in dimensional psychopathology compared to qualitative differences in categorical psychopathology. A major epistemological question here for ICD-11 and DSM-V is whether a categorical (atheoretical descriptive psychopathology) or a dimensional (functional psychopathology) approach is more appropriate for identifying comorbidity and multimorbidity as well as whether a combined approach is superior to any single one. Such a combined approach may include the symptom dimensions approach adding information to the traditional categorical approach for their reclassification. It seems that the time for a scientific constructivism reconciling different epistemological poles in psychiatry has come (Aragona 2011).

The comorbid and multimorbid relationships and syndromal complexity should be understood and explained as a synchronous relationship as well as a causal chain of biological, psychosocial and behavioral processes working together. There are several complementary models that may help explaining comorbidity and multimorbidity relationships and may contribute to better psychiatric diagnostic classifications in the future.

The antecedent model proposes that a mental disorder contribute to the etiopathogenesis of another one via various psychobiological and psychosocial factors. This model includes predisposing pathogenesis: a mental disorder predisposes to another one (anxiety disorder or depression predisposes to alcohol/substance abuse disorder) as well as two or more disorders may predispose to each other (anxiety disorders, depression, alcoholism and other substance abuse disorders). According to infornet theory, anxiety is a signal of behavioral alarm that there is a possible danger while depression is a signal that the desired goals are not achieved and helps disengage behavior from unattainable or inappropriate goals (Hyland 2010). Anxiety and depression are caused by outputs from parallel as well as sequential processing networks involving many different biochemicals. According to some opinions axis II disorders also may predispose to axis I disorders.

The consequence model suggests that one mental disorder may arise as a result of another mental disorder or its treatment. Some mental disorders like depression may arise in some individuals with serious mental disorders like schizophrenia as an emotional response to diagnosis, treatment and the destruction of the future life prospects. Anxiety represents a large entrance to different mental and somatic pathology, while depression is a common response to various mental and somatic disorders.

Either the common pathogenesis or the shared determinants model suggests that two or more mental disorders may have an overlapping pathogenesis. An underlying biological mechanism may contribute to two or more disorders, e.g. low serotonin disorders (anxiety disorders, depression, OCD, impulse control disorders). This model generally suggests common biological mediators, pleiotropic effects of the same genes, psychosocial adversities, psychological traits, emotional distress and behavioral factors

like alcohol and drug abuse, bad diet etc. which may lead to both mental disorders and somatic diseases (Weissman 2006, Steptoe 2007). The fact that one genotype can have multiple phenotype manifestations and on turn around a single phenotype may have two explanations:
1. It may be the manifestation of multiple genes (Klerman 1990)
2. Two or more latent disorders may share a root cause (Borsboom et al. 2011)

Both explanations are to be taken into deep account when considering this model.

According to *the stress-diathesis or vulnerability-resilience model*, a genetic constellation and/or an early insult predispose the patient to a series of later abnormal reactions and pathological conditions, so various mental disorders may appear after life stress or allostatic overload as conditions expressing the shared diathesis. Diathesis refers to predisposition to disease/illness including constitutional, biological factors as well as psychological variables such as cognitive and interpersonal susceptibilities. Diathetic individuals may respond with abnormal or truly pathological reactions even to physiological stimuli which overactivate the physiologic system until the weakest part of it breaks down. 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 a disorder develops. 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.

The developmental model or *different stages of the same disease model* suggests that a mental disorder may be just a developmental phase of the other one, e.g. generalized anxiety disorder commonly progresses to depression (the helplessness-hopelessness theory) as well as axis II disorders may be subclinical or attenuated forms of Axis I psychopathology (Klerman 1990). For the time being, the multiaxial system is 'agnostic' regarding to a possible causative relationship for specific conditions in Axis I and Axis II (Klerman 1990).

The mixed disorders model and *the alternate manifestations model* in some cases may be an alternative to comorbidity and multimorbidity concepts (e.g. schizoaffective disorder and anxiety-depressive disorder instead of comorbidity of schizophrenia and bipolar disorder and comorbidity of anxiety and depression).

The multisystem diseases model may be also an alternative to the comorbidity concept in some cases. Some comorbid disorders interdependently related to each other may represent a multisystem disease or complex disorder.

Psychiatric comorbidity is a complex philosophical and epistemological issue involving the nature of psychopathology and disease entities, multimorbidity measures with the appropriate nosologic classification and data collecting and evaluating. The future research should be focused on functional boundary syndromes between major psychiatric disorders and on the boundary symptoms between normality and mental disorders. Many mental disorders share a number of homonymous symptoms related to major psychophysiologic systems or specific neural networks like intrinsic brain connectivity networks, default processing network, theory of mind and mentalising system, attachment system, reward-punishment system, central security and alarm system, sleep-wakefulness or rest-arousal system, stress-resilience (fight or flight) system, memory and learning systems, etc. In association with these psychophysiologic systems it could be possible to create neurobehavioral modules. Neurobehavioral modules or brain functional networks may serve as the target of different etiopathogenesis and disturbances of modules and/or their connections may be the basis of mental disorders. This approach may lead to giving up descriptive psychopathology and traditional classification of mental disorders and introducing a functional psychopathology or function-oriented modular approach (van Praag 1993, Aragona 2009c, Jakovljević et al. 2010 , Gaebel & Zielasek 2011). The use of a multidimensional, multiperspective and function-oriented modular transdisciplinary approach may

be useful in helping to characterize and understand the nature and structure of co-occurring syndromes and disorders.

CONCLUSION

Psychiatric comorbidity is a very intriguing issue and raises many fundamental questions about the nature of psychopathology and emerges as a test for psychiatric classifications systems. The tremendous implications of the high rate comorbidity and multimorbidity across all groups of mental disorders, the variability in treatment response, and the unpredictability of the course are likely to shake the very foundations of medical psychiatry. No consensus exists over the core problem of undersanding, identifying and differentiating comorbidity/polimorbidity and further research and debate are still needed. A new framework integrating the subspecialties in psychiatry and medicine is needed to address comorbidity puzzle. The fundamental nature of stirring up and shaking up of the concepts and practices in psychiatry merging on the horizon do not suggest a smooth road ahead .The future comorbidity and multimorbidity research should deconstruct existing mental and somatic disorder/disease/illness categories and start with bottom-up measures of key mental, neural and body systems including resilience, mitochondrial energy metabolism, components of the gut-brain and heart-brain axis, etc.

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