Emerging clinical trends and perspectives on comorbid patterns of mental disorders in research

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Key words

comorbidity, mental disorder, iatrogenic disturbances, illness behaviour, psychological well-being, clinical trials

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Abstract

Comorbidity is a well-established and documented phenomenon in mental disorders and medicine with heuristic value. The concept of comorbidity remains however poorly defined and lacks a comprehensive and coherent theoretical framework. There is a need to develop coherent methodological strategies in order to promote a fuller understanding of the implications of comorbidity and to exploit its potential value with regard to etiopathogenic and therapeutic issues. This position paper makes recommendations of improved methodological standards and procedures and discusses a range of options that can provide incremental information that is likely to improve therapeutic outcomes. *Copyright © 2013 John Wiley & Sons, Ltd.*

State-of-the-art: definitions and methodological issues

Epidemiological and clinical studies have well documented that individuals with at least one mental disorder are

typically affected by other disorders as well. Patterns of high comorbidity have been described within the spectrum of mental disorders and with patterns of somatic disorders. Thus it is not surprising that comorbidity has increasingly become a popular theme in psychiatry, clinical psychology

and medicine. Although comorbidity and its heuristic value has been recognized long ago, there is neither a consensus about its definition nor a comprehensive and coherent theoretical framework (Maser and Cloninger, 1990; Wittchen, 1996a, 1996b). Currently, the term comorbidity is used quite liberally in various ways. Despite the fact that co-“morbidity” refers implicitly to diseases or disorders (Latin: *morbus*), the term is used (i) simply to denote the overlap of psychopathological symptoms or (ii) syndromes, or (iii) diagnostic groups within mental disorders or (iv) with somatic conditions, with and without taking into account explicit clinical and nosological considerations and irrespective of whether the phenomena meet the criteria for a mental disorder or disease.

The variability in the definition, the assessment and ways used in comorbidity research are indeed puzzling and have led to substantial variation in findings across studies and an increasingly complex and confusing picture about the potential value of this concept. Consequently, there is the claim that comorbidity might simply be an artefact of our currently imperfect diagnostic conventions and its explicit diagnostic criteria (see DSM-III, APA, 1980; DSM-IV-TR, APA, 2000) that split previously broader diagnostic classes “artificially” into smaller subsets. Substantial criticism was expressed also with regard to the lack of evidence for clearly defined boundaries between disorders. Thus, the field is divided into “splitters” on the one hand that prefer the explicit criteria and the increase in specifically defined disorders, because of its greater precision and potential aetiopathogenic and clinical value, and the “lumpers” on the other hand that perceive many comorbidity patterns as artefactual and misleading preferring to reduce the number of diagnoses as much as possible. The latter position is shared by colleagues from various perspectives: Those who favour traditional nosological as well as the hierarchical models in classification, as well as those in search of more comprehensive main dimensions of psychopathology. This position paper makes an attempt to clarify the concept of comorbidity, provides methodological guidance and discusses potential future developments that might facilitate advances in basic and clinical research.

The phenomenon of comorbidity in the field of mental disorders was recognized long ago by Hippocrates: “A woman of Thasos became morose as the result of a justifiable grief, and ... she suffered from insomnia, loss of appetite ... she complained of fears and talked too much; she showed despondency and ... many intense and continuous pains” (Hippocrates, *Aphorisms V*) or “patients with fear ... of long standing are subject to melancholia!” (Hippocrates, *Epidemics III*). The more systematic scientific exploration of comorbidity however is a more recent

development, linked to the introduction of explicit descriptive, operational criteria for specific mental disorders (Spitzer *et al.*, 1978; DSM-III, APA, 1980) and associated shifts of paradigms in psychopathological research, such as the neo-Kraepelinian paradigm that has become dominant in many research centres around the world (Klerman, 1990). The first modern definition of comorbidity is typically attributed to Feinstein (1970, pp. 456–457), who suggested to use the term comorbidity for “... any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study.” Thus, he defined comorbidity in the context of treatment outcome research of specific disease entities and has drawn attention primarily to a longitudinal perspective of comorbidity. Boyd *et al.* (1984, pp. 988–989) defined comorbidity in statistical terms within analyses of epidemiological data on mental disorders defined by DSM-III criteria as “... the relative risk of a person with one disorder to receive the diagnosis of another disorder.”

Both definitions were subsequently broadened and modified in the seminal work of Burke *et al.* (1990) and Wittchen (1996a, 1996b) by suggesting the following working definition “Comorbidity can be defined as the presence of more than one specific disorder in a person in a defined period of time” (Wittchen *et al.*, 1996b, p. 9; Burke *et al.*, 1990). This definition emphasizes that the meaningful use of comorbidity:

- (a) should be confined to clearly defined descriptive classes of diagnostic categories (i.e. the diagnostic criteria as specified in the DSM-III and DSM-IV-TR),
- (b) requires to define and specify the range of diagnostic classes considered, as well as
- (c) the time-frame of reference that could be either a variously broad time window for current (two-weeks, four-weeks, six-months, 12-months) up to lifetime or any other time or age-related period.

Critical issues in the assessment of comorbidity

Feinstein (1970), however, when he introduced the concept of comorbidity, referred to any “additional co-existing ailment” separate from the primary disease, even in this case the secondary phenomenon does not qualify as a disease *per se*. Indeed, in clinical medicine the many methods that are available for measuring comorbidity are not limited to disease entities (de Groot *et al.*, 2003). Fava *et al.* (2012a) suggest that assessment of comorbidity in psychiatry should be based on a broad assessment, encompassing subsyndromal symptoms, illness behaviour, functional capacity and psychological well-being.

There is the need to solve a range of critical methodological issues for improved comorbidity research (Table 1).

Conceptual level

At the *conceptual level*, a lot of confusion in this area relates to the fact that the term comorbidity is frequently used to simply describe associations of psychopathological symptoms and syndromes of mental disorders, rather than restricting the term to descriptive classes of codified disorders. Confusion also results when comorbidity studies do not specify specific diagnostic algorithms and the degree to which they consider hierarchical diagnostic exclusion rules (for example major depressive syndrome instead of major depressive disorder). Thus, for a better understanding of such findings on comorbidity a clear specification is necessary whether none, some, or all of the many diagnostic exclusions and hierarchies have been considered. Our classificatory systems (DSM-IV-TR, APA, 2000; ICD-10, WHO, 1992) provide a complex set of symptoms, syndromes, and diagnostic exclusions (First *et al.*, 1990) which might all affect the resulting comorbidity figures as well as their interpretation.

Units of contents

In terms of *units of contents*, comorbidity findings vary dramatically depending on the type and number of diagnostic classes considered. For example, there is little comparability between findings due to differences in diagnostic coverage such as the number or type of mental disorders, the inclusion of somatic or personality disorders. Crude comorbidity percentages, unaccompanied by a description of the specific diagnostic method and diagnostic coverage as well as appropriate adjustment for chance agreement, are thus of little value. The more diagnoses are considered in the analysis, the greater is the likelihood of chance association.

Time window and accuracy of resolution

Comorbidity rates and implications of findings are also dependent on the time frame of assessment for each disorder. Some studies restrict the term comorbidity to pure cross-sectional syndromes and disorders, others prefer a 12 month or lifetime-ever approach. Further, few studies report specific definitions of cross-sectional diagnoses; thus it remains unclear whether the full diagnostic criteria

Table 1. Critical issues in the assessment of comorbidity

1. Conceptual level	(a) comorbidity = associations between descriptive classes of disorders in a given time frame (b) co-occurrence = cross-sectional associations between symptoms or syndromes (c) disorders as defined by classification systems (d) postulated subthreshold models (e) application of hierarchical rules (i.e. DSM-III-R, ICD-10)
2. Units of content	within and across any of the following groups (diagnostic coverage) (a) mental disorders and specific subtypes within disorders (b) personality disorders (c) somatic disorders (d) psychosocial impairments and disabilities or between any of the above
3. Time window	(a) cross-sectional (two-weeks, four-weeks, six-months, 12-months, etc.) (b) longitudinal (one year, three years, etc.) (c) lifetime (over the whole lifespan) (d) accuracy of temporal resolution
4. Assessment method	(a) unstructured (nosological) diagnoses (ICD-9) (b) loosely structured clinical diagnoses (DSM-III) (c) structured diagnostic interviews (SCAN, SCID) (d) standardized diagnostic interviews (DIS, CIDI) (e) specific comorbidity instruments (memory probes)
5. Design and analysis	(a) sampling procedure (b) correction for base rates (c) consideration of confounding factors (e) cross-sectional versus prospective-longitudinal comorbidity (f) longitudinal comorbidity trajectories (symptom progression)

Note: CIDI, Composite International Diagnostic Interview; DIS, Diagnostic Interview Schedule; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SCID Structured Clinical Interview for DSM-IV.

are met within the last two weeks, four weeks, six months, or even within a year. Another critical and poorly studied issue is the accuracy with which the overlap of two or more conditions as well as their sequence effects are assessed. In the study of the comorbidity patterns of anxiety and depressive disorders, many but not all authors use the convention that there should be a time difference of at least one year between two disorders to determine which is primary and which secondary. Only recently attempts have been made to use a more subtle discrimination of the sequence of comorbid conditions by using specific comorbidity modules. But such attempts still depend on the recall accuracy and attribution of the subject interviewed.

Assessment methods

A fourth critical area is the assessment strategy used to examine comorbidity phenomena. Findings suggest that standardized instruments such as the Composite International Diagnostic Interview (CIDI, WHO, 1990; Wittchen and Pfister, 1997) reveal higher rates of comorbidity than structured clinical interviews (i.e. SCID, First *et al.*, 1996) and 2–3 times higher rates than diagnostic checklists or clinical judgments.

There is some evidence that clinicians are more focused on the current state, neglecting prior history and disorders that are not reported by patients unless a comprehensive assessment is performed (Knappe and Hoyer, *in press*). There are also indications that semi-structured diagnostic instruments despite their increased efficiency might be more vulnerable to halo effects than standardized instruments (Frances *et al.*, 1990; Kessler *et al.*, 1994).

Design and analysis

Design differences and the statistical analytic strategy are further major sources of discrepancies in comorbidity research. Sampling strategy, design type (i.e. cross-sectional or longitudinal approaches) obviously affect comorbidity findings. Therefore pooled analyses, on the basis of sophisticated statistical methods that adjust and correct for these differences between studies, are of major importance (Merikangas *et al.*, 1996).

Explanations and models for comorbidity

It is the merit of epidemiological studies with more sophisticated statistical methods to have demonstrated in cross-national reanalyses of available data that comorbidity is not an artefact, but a stable phenomenon across settings and studies. There is also compelling evidence that comorbidity findings are specific for certain types of disorders, that could not be explained by chance (Weissman *et al.*, 1996; Merikangas *et al.*, 1996). These findings raise the question about the meaning and the potential clinical, etiological, pathogenetic, and therapeutic consequences of comorbidity.

In the case of comorbidity of two disorders, testable models might have a relatively simple structure, even when incorporating a number of additional variables (i.e. moderators) or when using time-event models. However, more complex comorbidity patterns will pose a range of methodological and statistical challenges. So far, four types of causal factors (Table 2) and four potential causal relationships (a–d) have been investigated:

- (a) One particular disorder A precedes another disorder B. This has been shown for example for various anxiety disorders increasing (4–6-fold) the risk for

Table 2. Types of causal factors in theories of psychopathology (adopted from Cloninger *et al.*, 1990)

<i>A. Stable susceptibility and protective factors</i>	
1. Heritable genetic factors	(a) specific for single disorders (b) non-specific risk factors
2. Acquired biological factors (trauma, toxicity)	(a) specific (b) non-specific
3. Familial psychosocial (social learning conditioning)	(a) specific (b) non-specific
4. Non-familial psychosocial (individual experience)	(a) specific (e.g. ballet training and anorexia) (b) non-specific (e.g. low socio-economic status)
<i>B. Transient preparative or supportive factors</i>	
1. Genetic (e.g. genes expressed at specific ages such as puberty)	
2. Non-genetic biological factors (e.g. toxins, weight loss)	
3. Psychosocial factors (psychodynamic, sociocultural, conditioning, cognitive)	

secondary depression and a malignant course of depression (Bittner *et al.*, 2004; Stein *et al.*, 2001; Beesdo *et al.*, 2007).

- (b) Either disorder (A or B) may *predispose* to the development of the other. Although there is not much empirical support for this, it should remain an important perspective, especially in the context of family genetic studies.
- (c) One or several *key antecedent factor* is specific for different disorders, such as factor A causing anxiety and mood disorders with different probabilities. Here some authors have suggested certain personality traits like neuroticism as risk factors for the development of either disorder (Andrews, 1996).
- (d) *One or more distinct antecedent* factors are active, such as X and Y causing A, and X and Z causing B. One example for this more complex interaction pattern is the symptom progression model for panic disorder.

To further advance the concept of comorbidity, a more systematic and structured strategy to collect such data appears essential. This will allow joint and well powered analyses to test systematically hypotheses that have the potential to inform about the boundaries of mental disorders, both on a descriptive as well as an explanatory level. The findings available so far have also underlined the usefulness of the comorbidity concept for a new way of looking into the longitudinal and developmental aspects of mental disorders, and possibly also their relationship to somatic conditions. The full exploration of mechanisms of comorbidity requires an interdisciplinary approach to investigate nosology, assessment, and underlying models of comorbidity, as well as study designs beyond the scope of clinical and epidemiological studies, which so far comprise the bulk of comorbidity research.

Advances needed to enhance the clinical utility of comorbidity

There have been several areas of comorbidity research particularly relevant to treatment and clinical management.

Comorbidity of mental disorders and treatment

There is strong evidence that the majority of all patients with mental disorders in clinical settings do not meet criteria for just one, but typically for several disorders (Wittchen, 1996b; Zimmerman *et al.*, 2002). The clinician is expected to choose the most appropriate treatment strategy for his/her patient, but he lacks any evidence-based guidance on what might be the most appropriate choice.

Randomized controlled trials are geared to conditions devoid of substantial comorbidity and disease-specific guidelines provide very limited indicators for patients with multiple conditions (Fava *et al.*, 2012a). Further, patients with one or more mental disorder frequently have additional, but diagnostically subthreshold conditions (Benedetti *et al.*, 2009) and – to complicate things further – might show behaviours or characteristics that are directly or indirectly affecting treatment choice and course of treatment (i.e. illness behaviour, functional disability) (Fava *et al.*, 2012a). Current diagnostic classification rules do not address the issue whether several concurrent comorbid conditions should be treated sequentially or simultaneously, and in what order, and empirical evidence from clinical treatment provides no guidance about it. If different treatments for the two comorbid conditions are available or required, it is necessary to organize and plan the sequence (Fava *et al.*, 2012a). Macroanalysis (a method for organizing the clinical problems that are not necessarily limited to diagnostic entities) and microanalysis (a detailed analysis of specific symptoms characteristics and presentations) have been suggested in such cases for clinical psychiatry and psychology (Emmelkamp *et al.*, 1994; Fava *et al.*, 2012a; Tomba and Bech, 2012). Macroanalysis allows performing hierarchical judgments on the links among concurring problems and syndromes. The advantage of such methods is that it allows the clinician to go beyond the diagnostic classification as well the disorder-based comorbidity concept by additionally including clinically significant subthreshold conditions and other psychological disturbances that may have a significant impact on treatment choice. Some features with potential relevance for patients with specific disorders are: illness behaviour (Fava *et al.*, 2012b), insight (Lincoln *et al.*, 2007), avoidance behaviour, experiential avoidance (Berrocal *et al.*, 2009), aggressive outbursts if symptoms occur (Rief *et al.*, 2010), mental pain (Tossani, 2013). (Note: for comorbidity of mental with somatic disorder, see Schumann *et al.*, 2013.)

Iatrogenic comorbidity

Treatment of mental disorders is not limited to simply reducing the symptoms of a mental disorder. It also entails identifying persistent side effects and induced-withdrawal effects that may result in the development of new temporally secondary conditions. Such drug-induced disorders occurring during treatment and those occurring during dose reduction or drug discontinuation (Chouinard and Chouinard, 2008) have been highlighted as a neglected area of research. Psychotropic drug withdrawal syndromes have been divided into three categories: (i) classical new

symptoms; (ii) rebound; (iii) supersensitivity symptoms (Chouinard and Chouinard, 2008).

Classical new symptoms

They are the classical type of substance withdrawal syndromes (SWS), described during withdrawal of narcotics, barbiturates and alcohol, but also of antidepressants, antipsychotics and anti-anxiety drugs. SWS consist mostly of physical symptoms, but also include symptoms like anxiety and insomnia, which were not present before withdrawal of the substance. They are usually short-lasting unless they lead to death.

Rebound

Kales *et al.* (1978) described first what he called “iatrogenic psychiatric disorder induced by withdrawal of psychotropic medications” associated with short half-life elimination during benzodiazepines withdrawal. He characterized the disorder by a sudden increase of primary insomnia in greater severity than the original insomnia before treatment. Later, Chouinard *et al.* (1983) reported another “iatrogenic withdrawal induced disorder type”, characterized by rebound anxiety of greater severity than the original anxiety and also associated with short-half life and potent benzodiazepines withdrawal. These two conditions, even though reversible and short lasting, lead to difficulty in diagnosis and treatment, considerably affect patients compliance, and cause greater suffering for the patient than the original disorder.

Supersensitivity

The third category was initially discovered through its association with tardive dyskinesia following long-term treatment with antipsychotic medications (Chouinard and Chouinard, 2008). Tardive dyskinesia, a movement disorder of extrapyramidal origin, was found to be caused by prolonged intake of antipsychotic drugs, and thought to be related to dopamine receptor supersensitivity following prolonged blockade. That is why it was classified among supersensitivity drug-induced disorders. The first disorder subtype described was dopamine supersensitivity psychosis, which also occurred after prolonged use of antipsychotic medications and could be associated with tardive dyskinesia (Chouinard *et al.*, 1978). While rebound syndromes are short lasting, supersensitivity disorders are generally long lasting and affect the characteristics and therapeutic response of the disorder that was originally treated, such as the resistance that may ensue with loss of therapeutic response during long-term antipsychotic treatment. Other known examples of these dopamine

phenomena are represented by the onset of tardive dyskinesia after long-term treatment with antipsychotic medications. In contrast, similar serotonin and noradrenaline supersensitivity induced disorders have been reported after the long use of selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs). The drug mostly implicated has been paroxetine (Fava and Offidani, 2011; Belaise *et al.*, 2012). Antidepressant drugs, particularly SSRI and SNRI, may cause withdrawal symptoms and long-term disturbances despite slow tapering (Fava and Offidani, 2011; Belaise *et al.*, 2012). Other clinical phenomena involve switching into mania that occurs with use of antidepressant drugs in a previously established unipolar depression (Berk *et al.*, 2010), and the resistance that may ensue with loss of therapeutic response during long-term treatment with antidepressant drugs or upon rechallenge with a drug that has been used in the past in the same patient (Fava and Offidani, 2011). The characteristics that derive from a patient therapeutic history have been defined as iatrogenic comorbidity (Fava *et al.*, 2013).

In conclusion, any of the actual psychotropic drug treatment, particularly after long-term use, increases the patients risk to experience additional psychopathological problems and disorders. This particular type of “comorbid” complications is clearly understudied and needs enhanced future research emphasis.

Understanding how social and cultural factors affect comorbidity

A fuller exploration of determinants and implications of comorbidity will profit from incorporating needs of patients and adopting a social-cultural perspective. Social and cultural factors deeply affect the individual patient in various ways. For example, social stressors (such as work-related factors and perspective of economic consequences of impaired mental health) and cultural stressors (such as stigmatization of psychiatric disorders) can affect quality and severity of psychiatric symptoms (Holma *et al.*, 2012; Verboom *et al.*, 2011). Additionally, these factors can affect physical symptoms (for example, impact of lifestyle on cardiovascular or metabolic diseases), which in turn have a complex influence on mental symptoms (Kroenke, 2003). In addition to affecting symptoms, social and cultural references shape *expectations* patients have about recognition, assessment, and treatment of symptoms, which in turn can affect patients' *function* and its relationship to expectations and symptoms (Ferrari and Russell, 2010).

Questions to be solved

What are the treatment implications of comorbidity?

There is little research about how to strategically proceed in comorbid patterns. There is evidence for example that in comorbid panic disorder with secondary major depression, the exclusive treatment focus of cognitive behavioural therapy on treating panic disorder with agoraphobia effectively reduces depressive symptoms leading to full remission in most patients (Emmrich *et al.*, 2012). Other times, treatment of one disorder does not result in the disappearance of comorbidity. For instance, successful treatment of depression may not affect pre-existing anxiety disturbances (Fava *et al.*, 2012a), and antidepressants response in depressive patients is worse if depression is accompanied with somatic and pain symptoms (Lin *et al.*, 2011).

What might be the role of patient preference in treating comorbid patterns?

The changed spectrum of health conditions (shifted toward ageing and chronicity) and the interindividual variabilities in health priorities suggest that the aim of treatment should encompass the patients personal goals and preferences, that may range from attainment of cure to prevention of recurrence, from removal of functional impairment to alleviation of symptoms (Tinetti and Fried, 2004). In the current absence of scientifically sound recommendations in many areas, there is a need to examine whether orientation according to patient preferences might result in better patterns of course and outcome than clinicians' intuitive decisions (Fava *et al.*, 2012b).

Are there common factors underlying comorbidity and multimorbidity?

The finding that many comorbid factors share to a varying degree similar or overlapping vulnerability and risk factors prompts the need to examine diagnosis-specific and shared etiologies that might better inform about the most appropriate treatment strategies according to mechanisms rather than psychopathological symptoms and disorders.

Can randomized controlled trials in comorbid patients provide guidance?

The traditional randomized controlled trial is the undisputed gold standard for assessing the effect of an intervention for a particular target diagnosis. Typically the most prevalent patterns of comorbidity are excluded. Thus, the results necessarily might not reflect the effects later on in real life patients with comorbid patterns,

creating a considerable translational hurdle. One should consider procedures and standards to conduct randomized controlled trials without such extensive exclusion rules to better reflect the true picture in clinical settings and consider alternative forms of trials. Further, one may wonder, whether the fact that failed or inconclusive drug randomized controlled trials are particularly frequent (Otto and Nierenberg, 2002) is due to lack of consideration of treatment history and comorbidity (Enck *et al.*, 2013; Fava *et al.*, 2013).

Gaps in comorbidity research

Lack of methodological standards and a conceptual framework

Current comorbidity research lacks methodological standards and a conceptual framework. The lack of consensus and harmonization regarding methods and design is a core obstacle to advance our knowledge regarding a better understanding of the frequency, the implications and the reasons for comorbidity. This problem applies to all areas of comorbidity research, but is particularly pronounced when it comes to (a) examining the implications for etiology, treatment and service provision, (b) comorbidity with somatic disease (see Schumann *et al.*, 2013) and (c) the incorporation of comorbid aspects that are currently understudied, such as the role of "iatrogenic" comorbidity. Within the spectrum of methodology the role of clinical judgment and clinical decision-making needs to be appraised to close the gap between research (typically based on instruments) and clinical application (clinical decision-making). Clinical judgment is often discarded as a non-scientific and obsolete method. Yet, in their everyday practice, psychiatrists use observation, description and classification, test implicitly explanatory hypotheses, and formulate clinical decisions. Clinimetrics, the science of clinical measurements (Fava *et al.*, 2012a; Bech, 2012) provides an intellectual home for the reproduction and standardization of the clinical intuitions.

Linking comorbidity to etiological psycho-neurobiological research

Putative psychological and neurobiological factors are rarely specifically examined in their value to explain the development of comorbidity patterns. Such factors could be studied from the perspective of the factor being specific for a single disorder, and/or being a non-specific risk factor. In line with vulnerability or diathesis-stress models, it seems to be helpful to differentiate generally between enduring and transient or situational factors. Both types

can be described as either vulnerability or protective precipitating or supportive factors. As enduring vulnerability factors, heritable genetic or family genetic factors have been discussed. From a cognitive-behavioural perspective, relevant factors can be derived from social learning theory, conditioning models and cognitive models for example, dealing with self-efficacy and coping style (Berrocal *et al.*, 2009). Psychosocial factors such as the life-event structure, social conditions and social support have frequently been discussed as potentially relevant enduring factors. Transient factors also include genetic and non-genetic biological factors, as well as more situational-specific cognitive-behavioural response patterns that might cluster around the fourth group of psychosocial factors, which can either be cultural or socio-demographic, or take the form of acute life events.

Lack of consideration of social-cultural factors and the patients perspective

There are considerable gaps regarding the role of social and cultural factors as well as patients perception and reaction to comorbidity and its evolution. These factors have been poorly studied so far although they may affect presentation of symptoms, the development of comorbidity, choice of treatment, responsiveness and prognosis (Bech, 2012; Tomba and Bech, 2012).

Lack of appropriate clinical trials designs

The current standard of therapeutic trial in medicine nowadays is represented by the large, multi-centre controlled randomized trial with very specific inclusion and exclusion criteria, but little attention to the clinical history of patients (Tomba, 2012). Not surprisingly, however, the findings are often difficult to interpret. During the last decade, clinical trial designs became simplified to standard randomized controlled trials, and clinical samples were more and more artificially restricted. Both steps limited scientific insight and generalizability of trial results (Rief *et al.*, 2009; Enck *et al.*, 2013). Series of smaller trials performed on patient populations selected on the basis of iatrogenic comorbidity or on disease subtyping, potentially combined with adaptive or sequential designs, could increase our insight in processes and treatment developments (Fava *et al.*, 2013). These small trials may actually provide important clinical information that is immediately helpful to the clinician encountering that specific patient, unlike the average undifferentiated patient of the traditional large trial. If we peruse the literature for clinical studies concerned with samples homogeneous for treatment history we may find out that we do not even have adequate information from observational studies or open

therapeutic trials. Similarly, there have been very limited research efforts comparing broad spectrum individualized treatments with standardized single focused approaches (Emmelkamp *et al.*, 1994).

Concluding remarks

Given the importance and heuristic value of comorbidity in clinical care, there is an immediate need to stimulate a concerted research agenda on various levels. Comorbidity research needs greater agreement on relevant constructs and measurement to enable a clearer conceptual framework. Generally agreed assessment standards covering established explicit diagnostic criteria and conventions will be essential though not sufficient. Assessment strategies in comorbidity research should incorporate a wider range of assessment domains (multi-level approach) as well as methods of organizing clinical material according to a hierarchical organization such as macroanalysis and microanalysis (Tomba and Bech, 2012).

There is pressing need of clinimetric research on clinical judgment. A first strategy is concerned with staging. It differs from the conventional diagnostic practice in that it does not only define the extent of progression of a disorder at a particular point in time, but also where a person is currently along the continuum of the course of illness (Cosci and Fava, 2013). A second approach involves building unitary concepts from apparently scattered phenomena. What is shared by syndromes such as anxiety, panic, phobic disturbances and irritability may be as important as the differences between them and conditions that are apparently comorbid could be part of the same clinical syndrome (Fava *et al.*, 2012a). A complementary strategy has to do with subtyping and differentiating within a diagnostic entity (Bech, 2010).

Such a broader approach would be the basis of joint analyses with large numbers of subjects/patients allowing with sufficient statistical power to model statistically the effects and interactions of a wide range of moderating factors. At the same time such a broader approach will be instrumental to link basic neurobiological research and paradigms within specific hypotheses about the development of comorbidity patterns. The translational clinical value of such an approach may be substantially enhanced by linkage to challenging clinical problems such as relapse, loss of treatment effects, treatment resistance (Fava and Offidani, 2011; Fava *et al.*, 2013).

Acknowledgements

This article was generated as part of the activities of the group of leading European experts on psychological research and intervention, in order to provide an assessment of the state-of-the-art of research in different domains, identifying major

advances and promising methods and pointing out gaps and problems which ought to be addressed in future research. A similar critical appraisal with partly similar conclusions is concurrently provided elsewhere (Schumann *et al.*, 2013) by the ROAMER work group “Biomedical research”. Experts in both work groups have been selected for their academic excellence and for their competence in the different units of analysis needed to comprehensively characterize particular symptom domains. Their contributions do not aim to be systematic reviews of the field but rather provide a well-informed opinion of the authors involved. They also do not represent official statements of the ROAMER consortium, but are meant to inform the discussion on psychological research and intervention in mental

disorders among interested stakeholders, including researchers, clinicians and funding bodies. Recommendations made in this issue will undergo a discussion and selection process within the ROAMER consortium, and contribute to a final roadmap, which integrates all aspects of mental health research. We thus hope to provide an informed and comprehensive overview of the current state of psychological research in mental health, as well as the challenges and advances ahead of us.

Declaration of interest statement

The authors have no competing interests.

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