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GUEST EDITORIAL

Clinical staging and Profiling of late-life anxiety disorders; the need for collaboration and a life-span perspective

Clinical staging and profiling is a diagnostic strategy that goes beyond the traditional dichotomy in medicine of merely focusing on the presence or absence of a disease. Disease staging extends this traditional dichotomy by defining where a patient lies along the continuum of the course of his or her particular illness. Successful examples include the general tumor, node, metastasis (TNM) classification in oncology, as well as the New York Heart Association (NYHA classes I–IV) functional classification system for patients with congestive heart failure. It enables clinicians to select treatments relevant to earlier stages because such interventions may be more effective and less harmful than treatments delivered later in the illness course. Profiling is a further refinement, as well as a necessary component of staging. Profiling refers to the characterization of a patient within a specific disease stage, which is relevant for its course and treatment choice. An example of profiling is estrogen receptor positivity in patients with breast cancer.

Staging was first devised to chart the course of diseases with a known, progressive nature. Examples are most forms of cancer and dementia (Rikkert *et al.*, 2011). Staging may also be helpful in disorders with a highly variable prognosis, such as depression and anxiety disorders (Hetrick *et al.*, 2008). In the case of anxiety and depression, the prognosis may vary from the patient experiencing only one relatively mild episode in their lifetime, to a chronic illness that pervades all aspects of life and may even cause premature death. In disorders with a variable developmental trajectory, it is important to match appropriate care to the stage of development of the disorder and the resulting needs of the patient. In the case of anxiety disorders, this would entail devising a staging model that is sensitive to the duration, severity, comorbidity pattern and resulting level of disablement, and care needs of patients. In other areas of medicine, staging models have also been developed for the level of development of the underlying disease process. Examples are the Braak staging model for Parkinson's disease and the ongoing development of staging models for dementia using neuroimaging and other biological markers (Dickson *et al.*, 2010; Leclerc and Abulrob, 2013). There are a number of biological markers that have been proposed as putative markers for disease progression in depression (Moylan *et al.*, 2013) and it may well be that many of these will in time prove relevant for anxiety disorders also. However, it is fair to say that the evidence for a staging model for anxiety disorders based on systematic evaluation of the underlying disease process is not currently in place. Therefore, it is, at this point in time, probably more appropriate to speak of clinical profilers to denote all variables that may help predicting whether a patient is likely to progress to further and more disabling stages of an anxiety disorder as this may help in choosing appropriate treatments.

In sum, staging and profiling creates a prevention and treatment oriented diagnostic framework that goes beyond our current diagnostic systems. The ultimate goal would be to prevent progression to more advanced stage or enable regression to an earlier stage in an individual patient.

The group working with McGorry *et al.* (2014) has proposed a general clinical staging model for mental disorders ranging from stage 0 (at risk, but asymptomatic state) through stage 4 (severe and unremitting illness). Stage 1 is defined as an initial stage of undifferentiated general symptoms of distress (stage 1a) followed by a state more suggestive of a specific psychiatric disorder (stage 1b). In his model, stage 2 represents a first episode of a circumscribed psychiatric disorder, which may be followed by the development of persistent symptoms, frequent relapses or ongoing impairment (stage 3). Similar to the examples found in oncology and cardiology, this framework implies a severe disease with a progressive course. Understandably perhaps, initial attempts to stage psychiatric disorders have focused on the most severe disorders, like schizophrenia and bipolar disorder (e.g. Cosci and Fava, 2013; McGorry *et al.*, 2014).

To date, clinical staging of anxiety disorders is merely an ideal picture of the future. Nonetheless, empirical data increasingly support the potential of a staging concept. Recently, latent class growth analysis of anxiety symptoms over two years identified three trajectories in a sample of 907 adult

patients suffering from panic disorder, agoraphobia, social phobia, and/or generalized anxiety disorder. A severe course, present in 15.4% of the patients in that particular study, can be seen as stage 4 of the general staging model put forward by the McGorry group. Interestingly, baseline severity, duration of anxiety and disability predicted a severe chronic course much better than DSM-IV categories (Batelaan *et al.*, 2014). Of eminent importance, however, is knowledge of biological, psychological and social risk, and protective factors that influence movement across stages, especially those amenable for current interventions.

With respect to anxiety disorders in later life, we must acknowledge that over 95% of older persons with an anxiety disorder do have an onset early in life (Kessler *et al.*, 2005). Consequently, late-life anxiety disorders are almost by definition classified as stage 3 (persistent symptoms or frequent relapse) or stage 4 (severe and unremitting illness). On the other hand, in clinical practice up to half of the older patients who seek help for anxiety disorders may have a late-onset type defined as a first episode at age 60 years or older (Hendriks *et al.*, 2012). Interestingly, the distinction between early versus late-onset panic disorders might be an interesting profiling factor relevant for the choice between cognitive-behavioral therapy (CBT) and drug treatment with selective serotonin reuptake inhibitors (SSRI). With respect to avoidance behavior, CBT significantly outweighed SSRI treatment in late-onset panic disorder, while treatment effects were similar in older patients with early-onset panic disorder. Conversely, treatment with an SSRI favored CBT when targeting agoraphobic cognitions in the early-onset type, while both treatment modalities were equally effective in late-onset panic disorder (Hendriks *et al.*, 2012). Furthermore, a randomized controlled trial has shown that a stepped care intervention (watchful waiting, CBT-based bibliotherapy, CBT-based problem solving therapy, drug treatment) prevents the onset of a full-blown depressive disorder as well as anxiety disorders in distressed older persons (Van t' Veer-Tazelaar *et al.*, 2009; 2011). In later life, mixed anxiety depression may thus be relevant for profiling anxiety disorders. Even more rigorously, one may even argue for joint staging models of mood and anxiety disorders in later life.

Unfortunately, clinical staging and profiling of anxiety disorders is still in its infancies. A prerequisite for adequate staging and profiling of anxiety disorders is the availability of a well-validated model for anxiety disorders. Proposed models, however, are merely based on expert opinion and/or face value and differ widely (e.g. Clarke *et al.*, 2012; Van Balkom *et al.*, 2012; Cosci and Fava, 2013). A first step forward would be a better insight in the evolution of distinct trajectories of affective symptoms agnostic to current classification systems. Subsequently, treatment studies should phenotype their patients in much more detail (at a biological, psychological, and social level) and should be large enough to examine predictors of outcome. Studies should not be confined to specific age groups, but preferably include all age groups. Such studies might be able to evaluate age as a specific profiling factor, as a first episode in later life might for example, be prodromal to a degenerative brain disease. Nonetheless, bridging the whole age range poses significant challenges on the measurements instruments as argued for in this special issue (e.g. see Gould *et al.*, 2014; Johnco *et al.*, 2014; and Mueller *et al*, 2014).

Ultimately, rigorous studies within the framework of clinical staging will facilitate the development of better treatment strategies and more efficient care models for older persons with anxiety disorders. We should not discourage ourselves, as this special issue shows late-life anxiety research is alive and flourishing. Moreover, clinical staging is not an end product, but an ongoing learning system that can always be further refined. Even in the field of oncology, not all cancers do have a staging system, while the best staging models in oncology are updated regularly. A prerequisite for further development would be more and much larger treatment trials, enabling the study of several predictors across different strata of potentially relevant profiling characteristics. As has been shown by the use of virtual reality to enhance CBT in later life (Grenier *et al.*, 2014), even the use of high-tech computerized modules should not necessitate excluding older patients from such large trials.

Conflict of interest

None.

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