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Review article

A critical overview of the clinical evidence supporting the concept of neuroprogression in bipolar disorder

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1. Introduction

The notion of clinical staging is widely used in medicine for disorders such as cancer, dementia, and liver disease, among others. In addition to providing information inherent to diagnosis, this paradigm is useful for defining "the progression of disease in time and where a person lies along the continuum of the course of illness", thus informing about prognosis and contributing to treatment selection (Berk et al. 2007a; McGorry, 2010; McGorry et al., 2006). A criterion intrinsic to clinical staging is that the natural history of the disorder evolves along a predictable temporal progression (Berk et al., 2014; Kapczinski et al., 2014).

Recently, two different models of clinical staging have been specifically designed for bipolar disorder (BD) (Berk et al., 2007a, 2007b; Kapczinski et al., 2009). Both of them state that illness features go through different stages from at-risk to more severe and disabling presentations, but they differ in the proxy measures used to assess illness progression: Berk et al. (2007a) take episode recurrences whereas Kapczinski et al. (2009) consider symptoms/functioning during euthymia (Table 1). Since the emergence of these models, copious amounts of narrative reviews proposing BD as a neuroprogressive illness have been published (Berk, 2009; Berk et al., 2011a, 2014; Cardoso et al., 2015; Cosci and Fava, 2013; Frank et al., 2015; Fries et al., 2012; Gama et al., 2013; Post et al., 2012; Rodrigues et al., 2014; Vieta et al., 2011, 2013). These reviews suggest a progressive clinical course in BD – in which there is a higher risk of recurrences and cognitive impairments as well as poorer response to treatment and functional outcome as a function of previous episodes – as one of the pillars on which the

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Table 1
Models proposed for staging in bipolar disorder.

Stage	Berk et al (2007a, 2007b).	Kapczinski et al (2009).
0	Increased risk of severe mood disorder (e.g., family history, abuse, substance use). No specific symptoms currently.	At risk for developing BD, positive family history, mood or anxiety symptoms without criteria for threshold BD.
1a	Mild or non-specific symptoms of mood disorder.	Well-defined periods of euthymia without overt psychiatric symptoms.
1b	Prodromal features: ultra high risk.	
2	First-episode threshold mood disorder.	Symptoms in interepisodic periods related to comorbidities.
3a	Recurrence of sub-threshold mood symptoms.	Marked impairment in cognition or functioning.
3b	First threshold relapse.	
3c	Multiple relapses.	
4	Persistent unremitting illness.	Unable to live autonomously owing to cognitive and functional impairment.

notion of neuroprogression is supported (Berk, 2009; Berk et al., 2011b, 2014; Cosci and Fava, 2013; Gama et al., 2013; Post et al. 2012; Rodrigues et al., 2014; Vieta et al., 2011, 2013). Moreover, sensitization, oxidative stress, proinflammatory mediators, and alteration of neurotrophins have been proposed as some possible neurobiological mechanisms underlying neuroprogression (Berk, 2009; Berk et al., 2011b, 2014; Fries et al., 2012; Post et al. 2012; Rodrigues et al., 2014; Vieta et al., 2011, 2013). These data were summarized in a recent report of the Staging Task Force of the International Society for Bipolar Disorders (ISBD) (Kapczinski et al., 2014).

However, some caveats regarding the aforementioned reviews should be noted. First, the approaches to the literature tended to be held in a selective fashion as explicitly stated in one study (Post et al., 2012). That is, they focused on evidence in favor -but *not* against- of the progressive clinical course of BD. On the other hand, some methodological limitations were not entirely considered when interpreting the findings of the studies reviewed, which might have led to an over-interpretation in favor of the alleged progressive clinical course of the disorder. Then, we aimed to conduct a narrative review focused on the clinical evidence considered in previous studies as supporting the concept of neuroprogression in BD, but highlighting some aspects of the interpretation of the results and, sometimes, supplementing their findings with data usually not considered.

2. Methods

We reviewed the available evidence on the longitudinal course of BD concerning any of the following clinical domains: (i) episodes recurrences, (ii) cognitive functioning, (iii) functional outcome, and (iv) response to treatment. First, we decided beforehand to include the clinical studies acknowledged as being "in favor" of the hypothesis of neuroprogression in previous reviews (Berk, 2009; Berk et al., 2011a, 2014; Cardoso et al., 2015; Cosci and Fava, 2013; Frank et al., 2015; Fries et al., 2012; Gama et al., 2013; Post et al., 2012; Rodrigues et al., 2014; Vieta et al., 2011, 2013). However, for the purpose of this report, we complemented those studies with additional material derived from literature search of relevant publications and with focus on the longitudinal clinical course of BD. To that end, articles published in peer-reviewed English language journals between 1980 and 2015 were retrieved from the online databases Pubmed/PsycInfo using the terms bipolar and "staging", "progression", "neuroprogressi*", "episodes recurrenc*", "cycle length", "neurocognit*", "neuropsychol*", "functioning", "response to treatment". The reference lists of the studies identified for inclusion were also reviewed for further relevant reports. The aim of this additional material was not to be exhaustive but to highlight key studies that have contributed to our current understanding of the longitudinal clinical course of BD and to identify areas of uncertainty that could require future research.

3. Results

3.1. Episode recurrences and neuroprogression

One of the arguments used in previous narrative reviews to support neuroprogression in BD is that, with each successive episode, a phenomenon of cycle acceleration occurs. This is characterized by shortening of periods of wellness and a rising risk of future recurrences – in some cases also referred to as a shortening of cycle length, which is the time between the onset of consecutive episodes – (Berk et al., 2014; Berk, 2009; Kapczinski et al., 2009; Post et al., 2012).

This assumption is usually based on Kraepelin's (1921) original observations about the course of BD: "… for the most part the disease shows the tendency later on to run its course more quickly and to shorten the intervals…". Nevertheless, studies conducted throughout the twentieth century have shown inconsistent results, with some supporting the concept of cycle acceleration and others not (for a review see Baldessarini et al., 2012). Moreover, classical studies demonstrating the reversibility of rapid cycling in BD also suggest that episodes do not appear to accelerate consistently over time (Coryell et al., 1992; Maj et al., 1994).

Likewise, narrative reviews usually cite a series of subsequent Danish studies (Kessing and Andersen, 1999; Kessing et al., 1998a, 1998b, 1999; Kessing et al., 2004b) as clinical evidence of neuroprogression. These studies were conducted using the Danish Psychiatric Central Research Register (a nationwide registration of all psychiatric admissions), which enabled to follow a large sample of patients since their first admission for manic-depressive psychosis (ICD-8) for a long period of time (from 1970 to 1993), during which each re-hospitalization was considered as a proxy for recurrence. The earliest of these studies showed that a higher number of episodes was associated with different measures, such as decreased time to recurrence or increased risk to recurrence in survival analysis, which suggests that cycle acceleration occurs in BD (Kessing et al., 1998a; Kessing and Andersen, 1999). It is important to emphasize that, despite the authors' knowledge regarding selection bias toward more severe forms of BD – i.e. BD type I requiring hospitalization – another study assessing definitions of sensitization in the same sample showed a progressive course only in 26.5% of the patients (Kessing et al., 1998b). Moreover, these and all previous studies were affected by an additional selection: if patients who have multiple episodes have a constant high risk of recurrence from the beginning of the disease, these patients may have an increasing influence with each successive episode because they would represent a higher proportion of the remaining sample. This bias is usually called 'Slater's Fallacy', in honor to the psychiatrist Eliot Slater who, in his seminal report based on the re-analysis of the sample of patients evaluated