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"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, 2007; 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; Rodriguez 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 notion of neuroprogression is supported (Berk, 2009; Berk et al., 2011b, 2014; Cosci and Fava, 2013; Gama et al., 2013; Post et al, 2012; Rodriguez 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;

Rodriguez 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 BD 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; Rodriguez 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., 2009, 2014; Kapczinski et al., 2009; Post et al., 2012).

This assumption is usually based on Kraepelin's original observations (1921) 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, 2004) 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 by Kraepelin, warned about this statistical artifact that could explain cycle acceleration (Oepen et al, 2004; Slater, 1938). Then, Kessing and colleagues used an extended Cox regression model to overcome this problem, a frailty model, in which patients with a large frailty value trended to have a high rate of recurrences after any episode, whereas patients with a small frailty value had a low rate of recurrences (Kessing et al., 1999). In this study, although in the initial analysis the risk of recurrence increased very significantly with the number of previous episodes for all BD patients (younger, older, men, and women), when the model was adjusted for frailty, statistical significance

remained only for older women (Kessing et al., 1999). Another study used a frailty model with a sample of unipolar and bipolar patients, who were admitted between 1959 and 1963 to the Psychiatric Hospital University of Zurich with an affective episode and followed up to 1997 (Kessing et al., 2004). In this study, the risk of recurrences increased with the number of episodes in the pooled sample of affective patients, but there was no association when the subgroup of patients having their first episode during the follow-up period was considered (Kessing et al., 2004a). Finally, another study assessed the rate of relapses (not recurrences) among a mixed sample of patients with major depressive and bipolar disorders (ICD-10) that had their first discharge during the period 1994-1999 (Kessing et al., 2004b). In this study the rate of relapse leading to hospitalizations increased with the number of episodes in women but not in men (Kessing et al., 2004b).

In addition, other authors also tested the hypothesis of cycle acceleration considering Slater´s Fallacy with opposite results. On average, in a sample of patients with BD type I or schizoaffective mania from the NIMH Collaborative Program on the Psychobiology of Depression, cycle length increased rather than decreased over a follow-up period of 10 years (Turvey et al., 1999). Likewise, in a sample of BD patients hospitalized for their first episode, the course was largely random or chaotic during a follow-up period of 6 years and only a minority of patients showed either cycle-acceleration or slowing, without changes in wellness intervals (Baldessarini et al., 2012).

3.2. Cognitive functioning and neuroprogression.

Several studies showed a positive association between the number of previous episodes and cognitive impairments in euthymic patients (for a review see Robinson and Ferrier, 2006). This relationship was corroborated in further studies like that conducted by López-Jaramillo et al. (2010), in which euthymic BD patients with more than three manic

episodes showed worse overall cognitive performance compared with those with only one episode of mania. Similarly, Torres and colleagues (2010) reported that patients after resolution of their first manic episode showed smaller impairments in verbal memory and executive functions than those reported in meta-analyses of samples of euthymic non-first episode BD patients. Thus, the authors of these studies have suggested that cognitive deficits increase with successive episodes in BD (Lopez-Jaramillo et al., 2010; Robinson and Ferrier, 2006; Torres et al., 2010). Then, this interpretation of the data was taken as evidence for a neuroprogressive nature of BD in subsequent narrative reviews (Berk, 2009; Berk et al., 2007a, 2011a; Cardoso et al., 2015; Gama et al., 2013; Kapczinski et al., 2009, 2014; Post et al., 2012; Rodriguez et al, 2014; Vieta et al., 2011). In example, Kapczinski's staging model suggests a progression from no cognitive impairments in the premorbid and early stages of illness, in which periods of euthymia are well defined, to severe cognitive impairments in later stages of the disorder (Kapczinski et al., 2009).

However, the notion of intact cognitive functioning among BD patients in early stages is based largely only in measures of general intelligence or equivalents. However, it does not necessarily mean that patients with BD display preserved neurocognitive functioning before illness onset, since it may be that only specific cognitive domains (i.e. executive functions, attention, or verbal memory), which are not entirely reflected in general intelligence or IQ measures, are impaired in the premorbid stage. In fact, preliminary evidence suggests that cognitive impairments in some specific domains are present in the first episode and might precede the onset of illness (for a review see Lee et al., 2014, Martino et al., 2015).

Additionally, it is important to emphasize that the consistent data about the relationship between cognition and number of previous episodes are based exclusively on cross-sectional studies and, therefore, the direction of causality cannot be clearly defined (Martino et al., 2013). Similar to Slater´s Fallacy, even if cognitive functioning was stable

throughout the course of the BD, this association would be observed if patients with greater cognitive impairments were those with the highest number of recurrences over the course of the disorder. In addition, the aforementioned narrative reviews do not take into account some preliminary evidence that suggests that cognitive impairment may be static rather than progressive in BD. First, although limited by the relatively short follow-up periods, early longitudinal studies tend to show that cognitive deficits are stable throughout the evolution of the disorder (for a review see Samamé et al., 2014). Moreover, several studies on cognition in elderly patients with BD have shown that the pattern and degree of cognitive deficits are similar to those reported in young adult patients (for a review see Samamé et al., 2013). Although the risk of selection bias should be considered (i.e. ., elderly patients with more severe cognitive impairment may have been excluded of these studies), these results also suggest indirectly that cognitive impairments tend to be stable throughout the longitudinal course of the disorder.

3.3. Functional outcome and neuroprogression.

Some recent studies have attempted to validate neuroprogression in BD from the relationship between the number of previous episodes and functional outcome measures, and they were then included in some of the narrative reviews on the topic (Berk et al., 2014; Gama et al., 2013; Kapczinski et al., 2014; Rodriguez et al., 2014). Using data from the Systematic Treatment Enhancement Program for Bipolar Disorder, Magalhães et al. (2012) found that a greater number of previous episodes was associated with poorer functioning and quality of life both in cross-sectional and longitudinal (12 months) analyses. Similarly, Rosa et al. (2012) found that BD patients with their first episode experienced better functioning compared to patients with multiple episodes. These studies suggested that “functional impairment may be a consequence of enduring neurotoxicity of mood episodes and consequent neurostructural

abnormalities" (Rosa et al., 2012). However, this kind of interpretation contrasts with studies reporteing that a considerable percentage of patients do not achieve adequate functional recovery after their first episode (Keck et al., 1998; Strakowski et al., 1998; Tohen et al., 2003). On the other hand, it was reported that poorer psychosocial functioning (Gitlin et al., 1995) and residual symptoms at recovery (Perlis et al., 2006) are significantly associated with time to recurrences. Altogether, patients who do not achieve adequate functional recovery after their first episodes may be at a higher risk of future recurrence, suggesting that the relationship between the number of episodes and functioning is latent from the onset of the disorder.

In another recent study, Rosa et al. (2014) subdivided a sample of 54 patients into 4 subgroups, each corresponding to a different stage of Kapczinski's model. The authors reported that patients in later stages of the illness had worse results on the Functioning Assessment Short Test and greater cognitive deficits than patients in early stages. However, taking into account that the clinical stages described by Kapczinski are defined on the basis of patients' functioning during euthymia, and the known relationship between functional outcomes and cognitive deficits, these findings are somewhat circular and it is not possible to infer neuroprogression from them.

3.4. Response to treatment and neuroprogression.

Another argument used in previous reviews to support the notion of BD as a neuroprogressive disease is that successive episodes would induce treatment resistance (Berk, 2009; Berk et al., 2011b, 2014; Gama et al., 2013; Kapczinski et al., 2014; Post et al., 2012; Rodriguez et al., 2014). This type of statement is based on studies like that conducted by Swann et al. (1999), in which there was poorer response to lithium (but not to divalproex) in patients with many previous episodes. Similarly, a late non-response to lithium prophylaxis was shown in patients with higher number of previous episodes and hospitalizations (Maj et

al., 1996). Another study reported that response to lamotrigine was negatively correlated with the number of previous episodes (Obrocea et al., 2002). A similar pattern was also observed with antipsychotic medications. Pooled data from mania, depression, and maintenance studies of olanzapine funded by Eli Lilly & Co were analyzed by Berk et al. (2011a). Patients with mania with 1-5 previous episodes had better response than those who had >10 previous episodes, whereas there was no difference in response between previous-episode categories in studies of depression. Likewise, there was a 40-60% reduction in the risk of relapse into mania and depression in patients with 1-5 previous episodes compared with those with >10 previous episodes. Authors pointed out that their findings supported "an active process of neuroprogression in BD that is neurotoxic and that has the capacity to adversely impact treatment outcomes" (Berk et al., 2011a). Finally, a series of studies on psychosocial interventions showed a similar relationship with the number of previous episodes. Scott et al. (2006) found that adjunctive cognitive-behavioural therapy was more effective than treatment as usual only in patients with less than 12 previous episodes. Moreover, Reinares et al. (2010) showed that family psychoeducation was beneficial only in patients who had no functional or clinically relevant impairment and lack of symptoms confined to psychiatric comorbidity (Stage I of Kapczinski's model). On the contrary, there are studies that failed to find any association between number of previous episodes and pharmacological or psychosocial treatments (Baldessarini et al., 2003; Franchini et al., 1999; Lam et al., 2009; Magalhães et al., 2012).

Although "positive" studies are usually cited to support the notion of neuroprogression in BD, their results do not necessarily reflect a progressively evolving nature of the disorder. It was suggested that higher frequency of episodes and hospitalizations, rapid cycling, and concomitant drug abuse are likely to be predictors of poorer outcome of BD *per se* rather than specific predictors of unfavorable response to some type of treatment (Maj, 2000). Then, again here, Slater´s Fallacy should be considered. That is, those patients with more risk of recurrences -from the beginning of the illness- would be less responsive to treatment and

therefore be overrepresented among patients with higher number of previous episodes (even if the disorder was not progressive). Hence, these findings could only mean that patients with more severe forms of the disorder are less responsive to treatment, which occurs with almost all diseases in medicine.

4. Discussion.

There is a dearth of studies specifically designed to assess whether BD is a progressive condition. The only exception might be several reports exploring the association between successive episodes and increased risk of recurrences, although most of them were conducted only in hospitalized patients with BD type I. Results are not fully consistent with regard to the increase or decrease of cycle length over the course of the disorder (Baldessarini et al., 2012; Kessing et al., 1999; Kessing et al., 2004a; Kessing et al., 2004b; Turvey et al., 1999). It is possible that cycle acceleration occurs in a subset of 25 to 40% of this population as suggested by studies using different measures of progressive course (Baldessarini et al., 2012; Kessing et al., 1998b), while most patients could have a random or chaotic course. Conversely, there is no evidence of cycle acceleration in any of the other forms of the bipolar spectrum, which could be the focus of future studies. On the other hand, most of the findings from which the clinical concept of neuroprogression in BD has been built come from cross-sectional studies comparing patients with many and few previous episodes in relation to neurocognitive, functional or treatment outcomes. However, as mentioned throughout this review, even if these clinical features were stable over the course of the disorder, patients with many previous episodes would have poorer cognitive/psychosocial functioning and response to treatment than patients with few previous episodes. Therefore, it would be inadequate to consider the results of this approach as evidence of neuroprogression. On the contrary, only longitudinal studies in which a given therapeutic intervention has decreasing efficacy or

cognitive impairments worsen along successive recurrences could conclusively show the existence of progression. Unfortunately, this type of study has not been conducted to date. The role of functional outcome as evidence of neuroprogression could be more difficult to interpret. In fact, even if further longitudinal studies described functional deterioration in a subgroup of patients over the course of illness, it would be important to consider that this outcome could be reflecting the cumulative impact of adverse social factors, such as unemployment, lack of family or social support, or stigma among others, rather than reflecting the impact of underlying biological mechanisms. Regardless of the variable considered, it could be very advisable to employ incidence samples rather than prevalence samples to improve the generalizability of the results in further studies (Cohen and Cohen, 1984). Likewise, samples should ideally not be restricted to patients with BD type I, but include patients with other forms of the bipolar spectrum.

On the other hand, the existence of subgroups within BD cannot be discounted when describing the longitudinal clinical course of the disorder. As already mentioned, there may be a subgroup of patients not exceeding 25-40% that could show phenomena of cycle acceleration (Baldessarini et al., 2012; Kessing et al., 1998b). Moreover, there is growing evidence that about one third of euthymic BD patients have more severe cognitive deficits than usually reported in the literature, while a similar proportion are indistinguishable from healthy controls in terms of cognitive functioning (Burdick et al., 2014; Martino et al., 2014). Also, a similar percentage of BD patients could have poorer response to treatment and impaired functional outcome (Keck et al., 1998; Tohen et al., 2003). Taking into account the interrelationship between these variables, it is possible that the convergent results of these various studies indicate that the same subgroup of about one third of patients has most of these features: increased risk of recurrence and cognitive deficits, and poorer response to treatment and psychosocial functioning. In fact, a recent study applied latent class analysis and identified two subtypes of bipolar patients: a functionally and cognitively impaired

multiepisode patients and functionally and cognitively preserved patients with low episode recurrence (Reinares et al, 2013). It has been hypothesized that these variations in clinical features among BD subjects might be due to quantitative or qualitative differences which could also be the focus of further studies (Martino et al., 2014). Quantitative differences would imply the existence of a continuum of severity from patients with these clinical features at one end, and patients of opposing characteristics at the other. Alternatively, the differences in clinical features between patients could be qualitative, reflecting subgroups of patients with distinct underlying pathophysiological processes. If this were the case, one would expect to find differences between these subgroups of patients at the psychopathological level or in their longitudinal course. Moreover, in that context, alterations in biomarkers and structural or functional neuroimaging might reflect differences in pathophysiological pathways among subgroups of patients rather than progression through different stages of illness as is often suggested (Berk, 2009; Berk et al., 2011b, 2014; Kapczinski et al., 2014; Post et al., 2012; Rodriguez et al., 2014; Vieta et al., 2011, 2013).

Altogether, there are multiple knowledge gaps and constraints to conclude in the light of current clinical evidence that BD is a neuroprogressive condition as suggested in previous reviews (Berk, 2009; Berk et al., 2011b, 2014; Cardoso et al., 2015; Cosci and Fava, 2013; Fries et al., 2012; Gama et al., 2013; Kapczinski et al., 2014; Post et al, 2012; Rodriguez et al, 2014; Vieta et al., 2011, 2013). Therefore, we should be extremely rigorous and cautious with the interpretation of the data, given that wrongly considering BD as “a neuroprogressive illness” might involve a number of serious negative consequences. First, an error of this nature would create an additional aggravating and stigma among people affected by a disorder which in itself is often chronic and recurrent. Likewise, some ethical concerns might arise from prematurely considering BD as a neuroprogressive condition. For example, one of the main benefits of clinical staging is to contribute to the physician s’ ability to select treatments tailored to each stage to prevent progression of the illness, assuming that early interventions

will be both more effective and less harmful than treatments delivered later in the course (Berk et al, 2007; McGorry, 2010; McGorry et al., 2006). From this perspective, it has been suggested that treatment in the prodromal stage (McGorry, 2010; McNamara et al., 2010), early and sustained prophylaxis (Post et al., 2012), or the neuroprotective effect of mood stabilizers (Berk, 2009) may prevent the progression to later stages of BD. Although all these approaches are very attractive to be tested, they might lead to some unnecessary and aggressive treatments if the assumption of neuroprogression of BD is wrong.

In summary, the clinical evidence supporting the concept of neuroprogression in BD is scarce and limited. It could be risky to convince us that BD is neuroprogressive before that the clinical evidence supporting this hypothesis was convincing. Therefore, further longitudinal studies are needed to clarify if BD patients (or a subset of them) have a progressive clinical course or not. Until this occurs, clinical staging models proposed for BD may be describing subgroups of patients according to the severity of their clinical course rather than the progression of the disorder at a particular point of time.

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Highlights:

1- Based on current evidence, clinicians might assume that cycle acceleration occurs in subset of patients with bipolar disorder.

2- They nor should assume a worsening of neurocognitive functioning and functional outcome or a lower response to treatment as part of the longitudinal course of bipolar disorder.

3- More empirical longitudinal research is required to inform clinicians about the longitudinal course of these clinical features in bipolar disorder.

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.