Staging of Bipolar Disorder

15

15.1 The Concept of Staging

After the revolution which was brought with the introduction of operationalized diagnostic criteria by contemporary classification systems, the reliability and the validity of psychiatric diagnosis were greatly improved. Following the improvement in categorical diagnosis, two new needs emerge. The first is to explore all aspects of symptomatology and quantify severity. This is a function addressed with the use of psychometric and neuropsychological tools. There is much improvement in this field although much remains to be done (see Chap. 14). The second and still unfulfilled need is to define and rate seriousness, progression, changes in physiology and damage made and the extent and the specific characteristics of the disease. 'Staging' is the term which defines this procedure and it can provide the clinician with a valuable tool to assist the treatment design.

The field in medicine where staging is most successful and enjoys great importance is that of clinical oncology. In cancer treatment, staging is a valuable tool which determines the treatment strategy and suggests the prognosis.

It is common that psychiatrists constantly use some kind of a staging system; however, all of these systems are informal and they derive from subjective and anecdotal personal clinical experience. A true scientific staging system would constitute a heuristic tool intending to position the patient on a gradient of stages from 'unsymptomatic but at risk' to 'end stage'.

In 1993, there was the first formal proposal for the staging of mental illness (Fava and Kellner 1993). Several attempts followed (McGorry 2007) and 20 years later, a significant literature on the feasibility of staging and usefulness and its limits in psychiatry is available (Cosci and Fava 2013; McGorry 2007, 2010a, b; McGorry et al. 2006, 2007, 2010; Yung and McGorry 1996, 2007; Vieta et al. 2011).

It is important to note that in psychiatry, the diagnostic reliability and validity does not lead to predictive validity in the majority of cases (Hickie et al. 2013). Different diagnoses might have similar prognosis and overlapping treatments and persons with the same diagnosis might have different prognosis and need radically

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different treatments. Staging is one of the concepts which come to fill the gap between diagnosis and prognosis.

The concept of staging if and when applied has a number of implications. Almost by definition, it suggests that early stages are easier to treat while later stages are rather refractory to treatment. Thus, these later stages might need the application of treatment options with more adverse events and higher risk and less overall benefit (Post et al. 2010).

15.2 Staging of BD

It is reasonable to assume that staging can be applied to any illness or disorder that tends to progress. Although there is an old debate whether BD is static or progressing, the predominant approach today is that it is progressive at least to the extent other mental disorders are and not as benign as thought in the past. A description of its long-term course is discussed in Chap. 3 of the current book.

A reliable staging model is long in place concerning schizophrenia (Insel 2010), but staging is still a matter of debate concerning mood disorders. The 'kindling effect' was an early effort on this direction and probably works well for unipolar depression (Kendler et al. 2000; Post 1992; Segal et al. 1996); however, BD is rather too complex so that a single factor, procedure or approach could be sufficient for its staging. Probably a single model of early and very late stages of BD is viable (McGorry et al. 2008; Baldessarini et al. 2014), but things become rather complex in the middle.

Furthermore, often things are not as simple and straightforward as they seem or we wish them to be. Some authors generalize the finding for trials on the usefulness of early identification of the prodromal symptoms of relapse (Perry et al. 1999) to suggest that a similar strategy would be appropriate and beneficial for the prodromal stage of the disease, but this is a completely different issue.

Additionally, a factor which complicates the staging concept itself as well as the staging models is the effect of medication. It is certain that medication reduces symptoms, but it is uncertain whether there are medications which are truly neuroprotective in the neurobiological sense. There are some authors who argue that lithium might be such an agent, but the data are inconclusive, especially when it is combined with typical antipsychotics (Fountoulakis et al. 2008c). On the other hand, it is certain that many pharmacological agents exert severe adverse effects on the general somatic health of patients thus perplexing their overall picture and maybe perplexing the staging. Even if we set aside the fact that the prodromal phase as we consider it today lacks both specificity and sensitivity, it is unknown whether early treatment (during childhood or adolescence) with any of the agents in use today will benefit or actually worsen the overall outcome of the disease since preventive efficacy is unknown and adverse effects probable.

15.2.1 Clinical Determinants of BD Staging

The earliest research contribution to the effort of staging BD was the description of the stages of mania in the early 1970s (see Chap. 2). Carlson and Goodwin not only

Table 15.1 List of the multiple clinical aspects of manic–depressive illness

1. Manic episodes
2. Depressive episodes
3. Mixed episodes
4. Subthreshold manic symptoms
5. Subthreshold depressive symptoms
6. 'Mixed' states and 'roughening'
7. Mood lability/cyclothymia/'personality-like' behaviour
8. Psychotic features
9. Predominant polarity
10. Frequency of episodes/rapid cycling
11. Neurocognitive disorder
12. Drug/alcohol abuse
13. Behavioural dependencies (e.g. gambling)
14. Comorbid anxiety and other mental disorders
15. Comorbid somatic disorders
16. Self-destructive behaviour and suicidality
17. Functional deficit and disability

described discrete stages in the development and course of acute mania, but also they described a 'rollback phenomenon', that is, the clinical condition improves by manifesting the same stages but at a reverse order (Carlson and Goodwin 1973). Fava and colleagues proposed a somewhat different staging model for acute mania which included a prodromal personality-like stage, one hypomania and one mania without psychotic features stages and a psychotic mania stage (Fava and Kellner 1993). However, the description or the staging of acute episodes has a minor influence on the staging of the complete picture and the long-term course of BD.

If one takes the whole constellation of features and symptoms of BD into consideration (Table 15.1), he will realize that a staging system should include all these features and consider their position in the long-term course of the disorder and their relationship to treatment response, overall outcome and disability. The major features are acute major mood episodes, subthreshold and personality-like symptoms, psychotic features, predominant polarity, frequency, the neurocognitive deficit and comorbidity.

It seems that manic and depressive episodes load BD patients each with a different kind of burden and they push different pathways in the advancement of the disease. Mixed episodes sometimes resemble manic and sometimes resemble depressive episodes. Probably the predominant polarity, after several years, eventually turns to be depressive in the majority of patients (Alessandra et al. 2013; Garcia-Lopez et al. 2009; Popovic and Vieta 2013), while subsyndromal depressive symptoms dominate the inter-episode intervals, often since the beginning of the illness. Thus, depression is usually always present while the tendency to relapse into a manic episode seems to wane with the advancement of the disease. Even subsyndromal depressive symptoms cause significant disability (Judd and Akiskal 2003) and they put the patient at a three-time higher risk to relapse (Judd et al. 2008). Therefore, it seems it is depression that is mainly responsible for the burden of the disease (Judd et al. 2002, 2003; Goodwin and Jamison 2007).

Later in the course of the illness, with repeated acute episodes and with the increasing duration of the disease, the neurocognitive functioning worsens (Lewandowski et al. 2011; Clark et al. 2002; Cavanagh et al. 2002; Lebowitz et al. 2001; Zubieta et al. 2001; Denicoff et al. 1999; El-Badri et al. 2001; Reinares et al. 2010). One study reported that good vs. poor outcome groups, corresponding to early and late stages of BD, differed in terms of two underlying dimensions: illness severity and neurocognitive function (Reinares et al. 2013). More precisely it seems that manic episodes as well as psychotic features are those which load the patient with most of the neurocognitive deficit (Lewandowski et al. 2011). Depressive episodes also increase the neurocognitive impairment but to a lesser extent in comparison to manic episodes (Robinson and Ferrier 2006). There are data implying that the neurocognitive deficit might not progress after a specific stage (Strejilevich and Martino 2013).

Psychotic features seem to be a very important element which is related more with manic episodes. However, even in the frame of bipolar depression, psychotic features constitute a stable trait which tends to repeat itself across episodes (Helms and Smith 1983; Nelson et al. 1984; Aronson et al. 1988a, b).

The place of cyclothymia and dysthymia on this life-chart-based staging method is unknown, although cyclothymia is used in the already proposed staging models as an early prodromal phase (Cosci and Fava 2013; Berk et al. 2007a, b).

Rapid cycling is a complicated issue. Probably rapid cycling patients experience a higher number of major mood episodes in comparison to non-rapid cyclers, and this adds to the overall burden. The role of the number of episodes has been solidly proven by a number of authors (Torres et al. 2010; Vieta et al. 2013; Lopez-Jaramillo et al. 2010; Rosa et al. 2012; Post et al. 2003, 2010; Tohen et al. 2010; McGorry 2010a) and this is also the conclusion from an analysis of STEP-BD data which suggested that the number of previous episodes can be used as a reliable and valid proxy of staging (Magalhaes et al. 2012a). On the other hand, it seems that rapid cycling is state rather than trait and might not be valid as a long-term indicator (Carvalho et al. 2014). It is not known whether rapid cycling disappears as a process or it is overwhelmed by the domination of other stronger features, e.g. chronic unremitted depression. Chronic depression also determines to a significant extent the overall refractoriness, mainly because the available treatment options for bipolar depression are limited in comparison with those against mania (Fountoulakis et al. 2008b, 2011; Fountoulakis and Vieta 2008; Fountoulakis 2009).

Probably the only reliable prodromal syndrome is the presence of clinical anxiety in high-risk adolescents which increases the age-adjusted risk for the development of mood disorder from 40 to 85 % (HR = 2.6) with a similar increase in the risk for comorbid substance abuse during or after the development of the acute mood episode (Duffy et al. 2010).

A graphic representation of the important clinical features and their longitudinal possible relationship to the stages of BD is shown in Fig. 15.1. Probably the curves presented in this figure include also oscillations, but this feature was omitted for the sake of simplicity. On the basis of clinical data, it seems that three major stages can be identified, in addition to the at-risk and prodromal phase. The first stage includes a rather benign course with acute episodes of balanced polarity without psychotic features, good neurocognitive function, good response to treatment and also probably spontaneous remission. Important elements at this stage are the low frequency of inter-episode residual symptoms and good overall functioning without disability. On

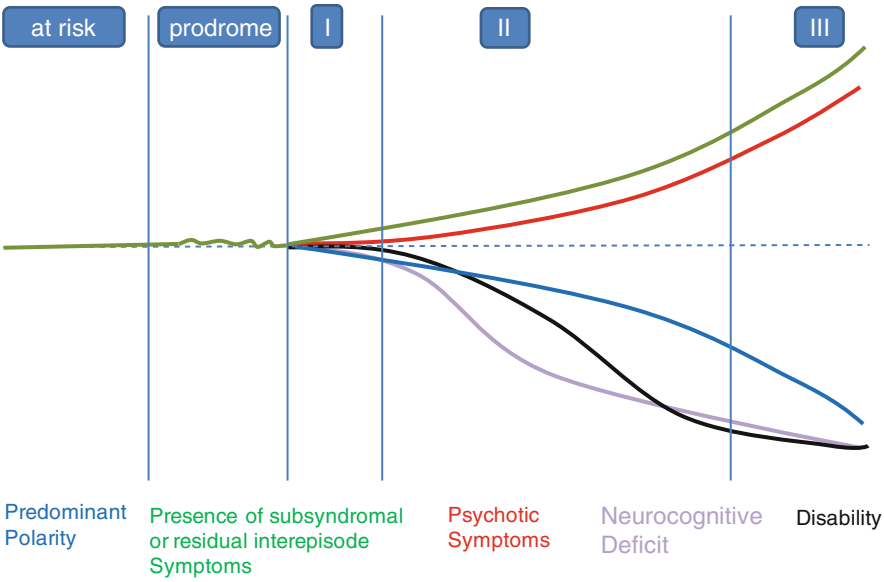

Fig. 15.1 A graphic representation of the important clinical features and their longitudinal possible relationship to the stages of BD. Probably the curves presented in this figure include also oscillations, but this feature was omitted for the sake of simplicity

the contrary, the third (last) stage is probably characterized by depressive predominant polarity with chronic refractory unremitted depression often with psychotic features, accompanied by a significant neurocognitive deficit and severe overall disability. Probably severe somatic comorbidity is present also, but this remains to be shown. These are in accord with research data which support the validity of the early vs. late stages in terms of differences in functioning and disability (Kapczinski et al. 2014; Rosa et al. 2012, 2014; Scott et al. 2013; Hamilton et al. 2011).

The middle stage is characterized by variability and probably it is composed by many different trajectories which reflect different combinations of clinical features and courses as well as comorbidities. Since many patients seek professional help only after they enter this stage, future research should focus mainly on this as well as in at-risk persons and the prodromal phase. One should have in mind that so far research has shown that risk factors and prodromal symptoms are non-specific and with low predictive value, maybe with the exception of anxiety in adolescents with positive family history (Fava 1999; McNamara et al. 2010).

15.2.2 Neurobiological Determinants of BD Staging

The neurobiology of BD is not well studied and the literature is rather limited in comparison to schizophrenia and unipolar depression. However, there is at least some data which suggests that a number of biomarkers differ in early- and late-stage BD (Kapczinski et al. 2009a).

15.2.2.1 Neuroimaging Data

BD is associated with a number of neuroimaging findings some of whom might have also some prognostic value. There are evidences suggesting that from the prodromal phase to the later stages of BD, there is an increased probability of structural brain changes that can be detected with neuroimaging (Lagopoulos et al. 2012; Strakowski et al. 2002).

The literature so far suggests that patients with BD manifest an enlargement of the third and lateral ventricles (Soares et al. 2005), white matter hyperintensities (Moore et al. 2001; Silverstone et al. 2003) and reduced grey matter in the prefrontal cortex, the hippocampus and the cerebellum (Moorhead et al. 2007; Soares et al. 2005; Blumberg et al. 2006). On the contrary an increase in the size of the amygdala might be present (Blumberg et al. 2006). The decrease in volume is generally correlated with the number of episodes (Strakowski et al. 2002) and generally these findings are considered to be associated with a poor prognosis (Moore et al. 2001; Silverstone et al. 2003).

Although, it should be noted that there is some degree of heterogeneity among studies concerning the specific areas which manifest atrophy or lesions; in general the findings concern the prefrontal, cingulate and subgenual cortices; the fusiform gyrus; and the left hippocampus (Lin et al. 2013; Javadapour et al. 2007; Fountoulakis et al. 2008a). On the other hand, there are reports suggesting that there was no difference in grey matter loss in BD patients in comparison to controls and there was also no effect of the number of episodes (Nery et al. 2009). In spite of findings concerning specific regions, it seems that the total brain volume remains stable, and this puts forward a number of problems concerning the methods of quantification of brain volume and other methodological issues (Fountoulakis et al. 2008a).

It is interesting that while in schizophrenia a loss of brain volume is evident already at onset, in BD this happens later. This is especially true concerning grey matter, while on the contrary, the loss of white mater volume might happen first and be present already at onset (Berk et al. 2010; Vita et al. 2009; Bora et al. 2010; Strakowski et al. 1993). Therefore, it is possible that white matter pathology is the prominent finding during the early stages (Lin et al. 2013), while grey matter loss follows years later (Arango et al. 2012).

Overall, the literature on neuroimaging data at different stages of BD is limited and most of the data are cross-sectional (Lim et al. 2013; Balanza-Martinez et al. 2005).

15.2.2.2 Neurochemical Data

The debate on the usefulness of peripheral biomarkers in psychiatry is several decades old; however, they are still considered to be important because they are conceptualized as mediators of allostasis and neurodegeneration (Juster et al. 2010; Kapczinski et al. 2008b; Berk 2009; Berk et al. 2011b).

Generally, it has been hypothesized that cellular mechanisms of resilience to stress are less efficient at later stages of BD (Fries et al. 2012). Research data suggest the levels of brain-derived neurotrophic factor (BDNF) (Cunha et al. 2008), neurotrophin-3 and neurotrophin-4 (NT3 and NT4) (Walz et al. 2007, 2009) and glial cell line-derived neurotrophic factor (GDNF) (Rosa et al. 2006) levels are reduced in BD patients.

An important study measured BDNF, tumour necrosis factor (TNF)-alpha and interleukin-6 and interleukin-10 levels in 60 BD-I patients and 60 matched healthy controls. It reported that BDNF was negatively correlated with the length of illness and was decreased only in the patients at the late stages of the disease. All the interleukins and TNF-alpha were increased already since the early stages, but interleukin-6 was not increased during the later stages. Also BDNF and interleukin-6 showed a relative decrease at the later stages in comparison to the earlier stages. TNF-alpha showed a further increase at the later stage. It seems that the decreases in the BDNF levels in BD patients are also age related (Yatham et al. 2009). Another study confirmed the finding that the levels of interleukin-10 decline in the late stages of BD (Rosa et al. 2014). These results are suggestive of a failure of those mechanisms responsible for the defence against the toxic effects of inflammation (i.e. BDNF) at later stages, while on the contrary, the inflammatory process persists (Kauer-Sant'Anna et al. 2009).

Further exploration of this sample also revealed a significant increase in 3-nitrotyrosine levels among all patients. The activity of glutathione S-transferase and reductase was increased only in the late-stage patients. Glutathione peroxidase activity and carbonyl content did not differ among the groups. These data are in accord with a possible tyrosine nitration-induced damage in BD patients that is present already since the early stages of the illness. The increased activity of glutathione S-transferase and reductase at later stages might suggest the activation of a compensatory mechanism (Andreazza et al. 2009). Also, serum thiobarbituric acid reactive substances and BDNF levels were found to be negatively correlated one to the other in BD patients but not in controls, suggesting that the lowering of BDNF levels in acute episodes occurs in parallel with increased oxidative stress, suggesting that such changes occur in an orchestrated fashion (Kapczinski et al. 2008a). The comparison of these patients to sepsis patients revealed almost similar levels of toxicity (Kapczinski et al. 2011). In partial disagreement with the above, a study in 115 BD patients and 25 first-degree relatives reported that increased interleukin-6 was associated with the late stages of the disease (Grande et al. 2014).

Similar conclusions were found by a study in 130 BD patients and 130 controls which reported that BD patients had significantly higher levels of inflammatory cytokines, including soluble interleukin-6 receptor (sIL-6R), soluble interleukin-2 receptor, C-reactive protein (CRP), soluble tumour necrosis factor receptor type 1 (sTNF-R1), soluble P-selectin receptor (sP-selectin) and monocyte chemotactic protein-1 (MCP-1). BD-II patients had lower levels of sTNF-R1 in comparison to BD-I. Also depressed patients had significantly lower levels of sTNF-R1 than the patients in manic/hypomanic episode and euthymic patients. These results in combination with the clinical data mentioned previously might suggest a role for sTNF-R1 in the staging of BD (Bai et al. 2014).

Two studies supported the hypothesis that mainly mania is associated with a proinflammatory state. The first one investigated serum high-sensitivity C-reactive protein (hsCRP) in manic, depressed and euthymic BD patients in comparison to controls and reported that the serum hsCRP levels were increased in manic patients in comparison to euthymic and depressed BD patients and controls. These results

are in accord with clinical data suggesting a specific neurotoxic effect of acute manic episodes (Cunha et al. 2008). In accord with this, the comparison of 61 BD patients with 25 controls in terms TNF-alpha, interleukin-2, interleukin-4, interleukin-6, interleukin-10 and IFN-gamma revealed that during mania interleukin-2, interleukin-4 and interleukin-6 were increased in BD patients in comparison with controls while depressed patients manifested an increase only in interleukin-6 levels and euthymic patients only in interleukin-4 (Brietzke et al. 2009).

The failure of protective mechanisms at later stages was confirmed by a meta-analysis which reported a correlation between the age and length of illness and serum BDNF (Fernandes et al. 2011). However, it seems that in spite of the more or less proper functioning of neuroprotective mechanisms during the early stages of BD, damage might start early. The assessment of serum protein carbonyl content (PCC) and thiobarbituric acid reactive substances (TBARS) suggested that BD patients had higher PCC levels than healthy subjects which is suggestive of a protein oxidative damage since the early stages (Magalhaes et al. 2012b). In another study the glial activity was assessed by measuring serum S100B content; the oxidative stress was assessed using serum TBARS and activities of antioxidant enzymes in BD patients during different episodes of the disease. The results showed that there was a significant increase of serum S100B during episodes of mania and depression, but not in euthymic patients. Superoxide dismutase (SOD) activity, as well the SOD/glutathione peroxidase plus catalase ratio, was also increased in manic and depressed patients. On the other hand, TBARS levels were increased in BD patients regardless of the phase of the disorder. These findings suggest a potential oxidative damage in BD patients with the mechanism being active mainly during the active phases of the illness but not during the euthymic phase. Such changes appear to relate to astrocyte function, as indicated by serum S100B elevation and thus they can also be related theoretically to brain MRI findings (Andreazza et al. 2007a).

The development of a 'systemic toxicity index' suggested that neurotoxicity was similar in patients under an acute manic or depressive episode and higher than in euthymic patients. The latter were similar to controls (Kapczinski et al. 2010; Magalhaes et al. 2011). An interesting finding was that the overall toxicity seemed to be attenuated in patients under medication treatment (Magalhaes et al. 2011). Another study reported that the levels of only SOD, catalase (CAT), alpha-linolenic acid and eicosapentaenoic acid (EPA) were significantly lower in BD patients, whereas glutathione peroxidase (GPx) was not (Ranjekar et al. 2003).

There is also a line of research indicating a significant damage in the DNA of BD patients in comparison to controls. The measuring of urinary excretion of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and 8-oxo-7,8-dihydroguanosine (8-oxoGuo) which are both markers of oxidatively generated DNA and RNA damage in 37 rapid cycling BD patients and in 40 age- and gender-matched controls revealed that the excretion of both was 40 % elevated in euthymic BD patients in comparison to controls. These results support the presence of an increased oxidatively generated damage to nucleosides in BD patients (Munkholm et al. 2014). Additionally the comparison of BD patients and controls in terms of the leukocyte mitochondrial DNA (mtDNA) revealed that the copy number was significantly lower

in the BD group suggesting that BD patients had significantly higher mitochondrial oxidative damage which was also positively correlated with age (Chang et al. 2014). Similarly, the investigation of 32 BD-I outpatients and 32 controls for DNA damage with the single cell gel electrophoresis comet assay revealed that there was an increased frequency of DNA damage in BD patients relative to controls, which correlated with the severity of symptoms of both depression and mania (Andreazza et al. 2007b). The measurement of the telomere length in 44 chronic mood patients and 44 controls revealed that the telomere length was significantly shorter in patients, representing as much as 10 years of accelerated ageing (Simon et al. 2006).

Overall, it seems there is considerable literature to support the hypothesis that in BD patients an inflammatory process exists, and it is combined at later stages with a deterioration of neurotrophic factors efficacy. The data so far imply that there is a combination of inflammation, oxidative stress, apoptosis and impairment in neurogenesis. This combination could result in the anatomical changes already mentioned above, probably via pro-apoptotic pathways, and the overall result is correlated with the number of mood episodes which exert a cumulative effect (Brietzke and Kapczinski 2008; Kapczinski et al. 2008b; Post et al. 2003). There are limited data supporting the idea that successful treatment could be neuroprotective and it could attenuate the neurostructural changes and postpone or even halt the progress on the disease (Berk et al. 2014).

So far there is one RCT which has shown the utility of the glutathione precursor N-acetyl cysteine which is a substance which might reinforce the role of the pathways of neuroprotection and neurogenesis (Berk et al. 2008).

15.2.3 Treatment Data Supporting the Staging Approach

The results of the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study which included 3,115 BD patients reported that significantly more first-episode patients achieved complete symptomatic and functional recovery in comparison to those patients with multiple episodes (Tohen et al. 2010).

A post hoc analysis reported that patients at an early stage benefited from caregiver psychoeducation by having longer time to recurrence, while there were no significant benefits from caregiver psychoeducation in patients at later stages (Reinares et al. 2010). Overall, this seems to be a generalized effect concerning psychotherapy in BD patients (Reinares et al. 2013; Scott et al. 2006) with 10–12 previous episodes probably constituting the cut-off. On the contrary, it seems that functional remediation could be more suitable for patients in advanced stages (Torrent et al. 2013).

The analysis of the pooled data from mania, depression and maintenance studies of olanzapine suggested that the response rates for the mania and maintenance studies ranged from 52 to 69 % and 10–50 %, respectively, for individuals with one to five previous episodes and from 29 to 59 % and 11–40 % for individuals with >5 previous episodes. For the depression studies, response rates were significantly higher for the one to five group for two measures only and the difference was less robust (Berk et al. 2011a). Similarly further studies support the suggestion that

lithium and olanzapine appear to be more efficacious during the early phases of the BD (Swann et al. 1999; Ketter et al. 2006) and maybe that higher lithium levels might be necessary to achieve a therapeutic effect after three or more mood episodes (Gelenberg et al. 1989).

15.3 Existing Models for the Staging of BD

There are five major staging models proposed concerning BD (Berk et al. 2007a, b; Kapczinski et al. 2009b; Post 2010; Frank et al. 2014; Cosci and Fava 2013; Post et al. 2012). In summary they are shown in Table 15.2 together with the possible accompanied clinical, neurobiological and treatment data as well as disability status.

15.3.1 The Model of Berk et al. (2007a, b)

Stage 0: *asymptomatic at-risk stage*

This stage refers to the period before the manifestation of any kind of symptomatology. It concerns persons loaded with potent risk factors for the development of BD, including family history of either BD or unipolar depression, history of pregnancy or obstetric complications, winter–spring birth, childbirth, early traumatic events and childhood history of physical or sexual abuse. Biological risk factors (endophenotypes) include circadian rhythms, response to sleep deprivation, white matter hyperintensities, response to psychostimulants, cholinergic sensitivity, P300 event-related potential abnormalities and changes in peripheral mononuclear cells. A history of substance abuse constitutes an additional risk factor.

Stage 1a and 1b: *prodrome*

During this stage, the patient experiences the onset of subthreshold symptoms (dysthymia, cyclothymia) or mood fluctuations and a variety of comorbid conditions and behavioural problems. Unfortunately and in spite of various proposals, currently there are no specific symptoms in the frame of depressive symptomatology to denote the onset of BD. The most promising seem to be the refractoriness to antidepressants and antidepressant-induced mania, hypomania or agitation. An additional problem is that this stage is not specific for BD.

Stage 2: *first-episode mood disorder*

At this point a formal diagnosis is made and proper treatment is essential. Unfortunately the first episode is most often depressive and the diagnosis of unipolar depression is put. This delays proper treatment until a manic or hypomanic episode emerges. Currently it is impossible to differentiate bipolar from unipolar depression in a reliable and valid way.

Stage 3b: *recurrence*

At this stage the diagnosis is firm, episodes alternate and polarity slowly turns into depressive. Response to treatment is variable and so is residual inter-episode symptomatology.

Table 15.2 A summary of the existing models for the staging of BD against the clinical, neurobiological and treatment data and disability as discussed in the current chapter

Stage	Berk et al.	Kapczinski et al.	Cosci and Fava	Post et al.	Frank et al.	Findings
At-risk	Stage 0: asymptomatic at-risk stage	Latent phase	–	Stage I–II	Stage 0	*Clinical*: asymptomatic *Neurobiology*: genes *Treatment*: unknown *Disability*: absent
Prodrome	Stage 1a and 1b: prodrome	–	Stage 1	Stage III	Stage 1a, b	*Clinical*: non-specific symptoms, anxiety *Neurobiology*: white matter hyperintensities *Treatment*: unknown *Disability*: absent
First episode	Stage 2: first-episode mood disorder	Stage I	Stage 2	Stage IV	Stage 2	*Clinical*: acute mania or major depression *Neurobiology*: white matter loss, inflammation mechanisms activated, neuroprotective mechanisms intact *Treatment*: good response to medication, psychoeducation recommended *Disability*: absent
Early phase	Stage 3b: recurrence	Stage I	Mainly stage 2, partially stage 3	Stage V	Stage 3a, b	*Clinical*: acute episodes of either pole, without or with minimal residual symptoms *Neurobiology*: white matter loss, probably grey matter loss, inflammation mechanisms activated, neuroprotective mechanisms relatively but not entirely intact *Treatment*: good response to medication, psychoeducation recommended *Disability*: mild

(continued)

Table 15.2 (continued)

Stage	Berk et al.	Kapczinski et al.	Cosci and Fava	Post et al.	Frank et al.	Findings
Middle phase	Stage 3b: recurrence	Stage II	Stage 3 and 4	Stage VI	Stage 3a, b	*Clinical*: acute episodes of either pole with significant residual symptoms, psychotic symptoms, neurocognitive decline *Neurobiology*: both white and grey matter loss. Inflammation process active, neuroprotective mechanisms gradually declining. Possible DNA damage *Treatment*: variable response to medication. Unknown which psychotherapy is more suitable *Disability*: moderate
Late phase	Stage 4: treatment resistance	Stage III and IV	Stage 3 and 4	Stage VII–VIII	Stage 4	*Clinical*: predominant depressive polarity, possibly with mixed and psychotic features, severe neurocognitive deficit *Neurobiology*: both white and grey matter loss, inflammation process active, neuroprotective mechanisms failing, DNA damage *Treatment*: refractoriness, recommendation for functional remediation *Disability*: severe

Stage 4: *treatment resistance*

The definition of treatment resistance is complex (Fountoulakis 2012); however, it seems that with the passing years and accumulation of episodes, BD patients develop a type of resistance to treatment. The duration of episodes is prolonged and residual symptoms (especially depressive) is the rule rather than the exception.

15.3.2 The Model of Kapczinski et al. (2009b)

Latent phase

This model puts significant emphasis in family history and more specifically on the genetic loading of individuals. Thus, it defines a first phase which includes asymptomatic persons at risk for developing BD. The recommended intervention is to avoid environmental factors which supposedly interact with genes to produce psychopathology.

Stage I

This model does not include a prodrome stage with subsyndromal symptoms. It proceeds to stage I which is characterized by full remission of episodes without any residual symptoms between episodes. This suggests a benign course of the illness and/or excellent response to treatment.

Stage II

This stage is characterized by the presence of inter-episode symptoms and comorbidities. Response to treatment is less good and impairment starts emerging.

Stage III

This stage is characterized by neurocognitive impairment and significant functional disability. Response to treatment is poor and complex strategies are needed.

Stage IV

Severe disability and neurocognitive impairment; unable to live alone.

15.3.3 The Model of Post et al. (Post 2010; Post et al. 2012)

Stage I

Initial vulnerability based on genetic or environmental impact

Stage II

The well-interval

Stage III

The prodrome

Stage IV

Illness onset with the occurrence of a full-blown episode

Stage V
Episode recurrence

Stage VI
Illness progression

Stage VII
Treatment refractoriness

Stage VIII
Late- or end-stage illness with catastrophic social, neurocognitive and medical deterioration and inability to care for oneself

15.3.4 The Model of Cosci and Fava (2013)

Stage 1
This stage corresponds to a prodromal phase and includes mild or non-specific symptoms of mood disorder and/or cyclothymia

Stage 2
It includes the development of full-blown major depressive or manic/hypomanic episodes

Stage 3
Concerns the presence of residual phase symptoms with marked neurocognitive deficit and disability in spite of treatment

Stage 4
Refers to refractoriness to treatment with the emergence of acute episodes despite mood-stabilizing treatment

15.3.5 The Model of Frank et al. (2014)

Stage 0
This state refers to an increased risk of BD in asymptomatic patients.

Stage 1a
This includes the presence of mild or non-specific symptoms.

Stage 1b
It refers to ultra-high risk. There are moderate but subthreshold symptoms present, with neurocognitive impairment and functional decline.

Stage 2
First full-blown episode of BD. Presence of neurocognitive deficits and functional decline.

Stage 3a
Incomplete remission from first episode.

Stage 3b
Includes the recurrence or relapse of psychotic or mood symptoms, but with good response to treatment. Presence of residual symptoms or neurocognition below the best level achieved following remission from first episode.

Stage 4
Severe, chronic illness with significant disability.

15.4 The Future of Staging of BD

A summary of the existing models for the staging of BD against the clinical, neurobiological, treatment data and disability as discussed in the current chapter is shown in Table 15.2.

There is broad consensus that staging of BD could be proven valuable both in the prevention and in the development of more efficacious and appropriate treatment of BD (McIntyre and Correll 2014); however, there is important controversy as to how far we can go on the basis of existing data.

Although there is some support for the proposed staging models, the research base is thin, the heterogeneity of the data is significant and the studies include small numbers. A number of vicious logical cycles could be in place. Most of the data are cross-sectional (Kapczinski et al. 2014) and the need for a transdiagnostic and longitudinal research approach is prominent (Lin et al. 2013).

The data so far support the presence of an asymptomatic at-risk phase and of a non-specific prodromal phase. This prodromal phase seems to be common for a number of mental disorders and prediction is impossible on the basis of current knowledge. The literature is also supportive of the presence of an early stage of the full-blown illness, during which the episodes are well defined, there are no or very few inter-episode residual symptoms, there is good response to treatment and there is little disability. It is also in support for the presence of a late stage which is associated with a more chronic and refractory disease, probably with depressive predominant polarity, psychotic features and significant disability. It is disappointing that there is little research on the treatment effect at late stages (Berk et al. 2012).

Future research should utilize a longitudinal prospective design in order to chart in detail the clinical picture (including neurocognitive function and disability) as well as the neurobiological changes that occur in the long-term course of BD and their relationship with the response to treatment. Such an approach will provide with valuable information on how to best stage BD and how to best design the therapeutic intervention.

References

Alessandra MA, Colom F, Pacchiarotti I, Murru A, Scott J, Valenti M, Mazzarini L, Mar Bonnin CD, Jose SM, Serretti A, Vieta E (2013) Treatment strategies according to clinical features in a naturalistic cohort study of bipolar patients: a principal component analysis of lifetime pharmacological and biophysic treatment options. Eur Neuropsychopharmacol 23(4):263–275

Andreazza AC, Cassini C, Rosa AR, Leite MC, de Almeida LM, Nardin P, Cunha AB, Cereser KM, Santin A, Gottfried C, Salvador M, Kapczinski F, Goncalves CA (2007a) Serum S100B and antioxidant enzymes in bipolar patients. J Psychiatr Res 41(6):523–529. doi:10.1016/j.jpsychires.2006.07.013

Andreazza AC, Frey BN, Erdtmann B, Salvador M, Rombaldi F, Santin A, Goncalves CA, Kapczinski F (2007b) DNA damage in bipolar disorder. Psychiatry Res 153(1):27–32. doi:10.1016/j.psychres.2006.03.025

Andreazza AC, Kapczinski F, Kauer-Sant'Anna M, Walz JC, Bond DJ, Goncalves CA, Young LT, Yatham LN (2009) 3-Nitrotyrosine and glutathione antioxidant system in patients in the early and late stages of bipolar disorder. J Psychiatry Neurosci 34(4):263–271

Arango C, Rapado-Castro M, Reig S, Castro-Fornieles J, Gonzalez-Pinto A, Otero S, Baeza I, Moreno C, Graell M, Janssen J, Parellada M, Moreno D, Bargallo N, Desco M (2012) Progressive brain changes in children and adolescents with first-episode psychosis. Arch Gen Psychiatry 69(1):16–26. doi:10.1001/archgenpsychiatry.2011.150

Aronson TA, Shukla S, Gujavarty K, Hoff A, DiBuono M, Khan E (1988a) Relapse in delusional depression: a retrospective study of the course of treatment. Compr Psychiatry 29(1):12–21

Aronson TA, Shukla S, Hoff A, Cook B (1988b) Proposed delusional depression subtypes: preliminary evidence from a retrospective study of phenomenology and treatment course. J Affect Disord 14(1):69–74

Bai YM, Su TP, Tsai SJ, Wen-Fei C, Li CT, Pei-Chi T, Mu-Hong C (2014) Comparison of inflammatory cytokine levels among type I/type II and manic/hypomanic/euthymic/depressive states of bipolar disorder. J Affect Disord 166:187–192. doi:10.1016/j.jad.2014.05.009

Balanza-Martinez V, Tabares-Seisdedos R, Selva-Vera G, Martinez-Aran A, Torrent C, Salazar-Fraile J, Leal-Cercos C, Vieta E, Gomez-Beneyto M (2005) Persistent cognitive dysfunctions in bipolar I disorder and schizophrenic patients: a 3-year follow-up study. Psychother Psychosom 74(2):113–119. doi:10.1159/000083170

Baldessarini RJ, Tondo L, Visioli C (2014) First-episode types in bipolar disorder: predictive associations with later illness. Acta Psychiatr Scand 129(5):383–392. doi:10.1111/acps.12204

Berk M (2009) Neuroprogression: pathways to progressive brain changes in bipolar disorder. Int J Neuropsychopharmacol 12(4):441–445. doi:10.1017/S1461145708009498

Berk M, Conus P, Lucas N, Hallam K, Malhi GS, Dodd S, Yatham LN, Yung A, McGorry P (2007a) Setting the stage: from prodrome to treatment resistance in bipolar disorder. Bipolar Disord 9(7):671–678. doi:10.1111/j.1399-5618.2007.00484.x

Berk M, Hallam KT, McGorry PD (2007b) The potential utility of a staging model as a course specifier: a bipolar disorder perspective. J Affect Disord 100(1–3):279–281. doi:10.1016/j.jad.2007.03.007

Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Bush AI (2008) N-acetyl cysteine for depressive symptoms in bipolar disorder–a double-blind randomized placebo-controlled trial. Biol Psychiatry 64(6):468–475. doi:10.1016/j.biopsych.2008.04.022

Berk M, Hallam K, Malhi GS, Henry L, Hasty M, Macneil C, Yucel M, Pantelis C, Murphy B, Vieta E, Dodd S, McGorry PD (2010) Evidence and implications for early intervention in bipolar disorder. J Ment Health 19(2):113–126. doi:10.3109/09638230903469111

Berk M, Brnabic A, Dodd S, Kelin K, Tohen M, Malhi GS, Berk L, Conus P, McGorry PD (2011a) Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. Bipolar Disord 13(1):87–98. doi:10.1111/j.1399-5618.2011.00889.x

Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, Yucel M, Gama CS, Dodd S, Dean B, Magalhaes PV, Amminger P, McGorry P, Malhi GS (2011b) Pathways underlying

neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev 35(3):804–817. doi:10.1016/j.neubiorev.2010.10.001
Berk M, Berk L, Udina M, Moylan S, Stafford L, Hallam K, Goldstone S, McGorry PD (2012) Palliative models of care for later stages of mental disorder: maximizing recovery, maintaining hope, and building morale. Aust N Z J Psychiatry 46(2):92–99. doi:10.1177/0004867411432072
Berk M, Berk L, Dodd S, Cotton S, Macneil C, Daglas R, Conus P, Bechdolf A, Moylan S, Malhi GS (2014) Stage managing bipolar disorder. Bipolar Disord 16(5):471–477. doi:10.1111/bdi.12099
Blumberg HP, Krystal JH, Bansal R, Martin A, Dziura J, Durkin K, Martin L, Gerard E, Charney DS, Peterson BS (2006) Age, rapid-cycling, and pharmacotherapy effects on ventral prefrontal cortex in bipolar disorder: a cross-sectional study. Biol Psychiatry 59(7):611–618. doi:10.1016/j.biopsych.2005.08.031
Bora E, Fornito A, Yucel M, Pantelis C (2010) Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. Biol Psychiatry 67(11):1097–1105. doi:10.1016/j.biopsych.2010.01.020
Brietzke E, Kapczinski F (2008) TNF-alpha as a molecular target in bipolar disorder. Prog Neuro-Psychopharmacol Biol Psychiatry 32(6):1355–1361. doi:10.1016/j.pnpbp.2008.01.006
Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'anna M, Mascarenhas M, Escosteguy Vargas A, Chies JA, Kapczinski F (2009) Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J Affect Disord 116(3):214–217. doi:10.1016/j.jad.2008.12.001
Carlson GA, Goodwin FK (1973) The stages of mania. A longitudinal analysis of the manic episode. Arch Gen Psychiatry 28(2):221–228
Carvalho AF, Dimellis D, Gonda X, Vieta E, McLntyre RS, Fountoulakis KN (2014) Rapid cycling in bipolar disorder: a systematic review. J Clin Psychiatry 75(6):e578–e586. doi:10.4088/JCP.13r08905
Cavanagh JT, Van Beck M, Muir W, Blackwood DH (2002) Case-control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. Br J Psychiatry 180:320–326
Chang CC, Jou SH, Lin TT, Liu CS (2014) Mitochondrial DNA variation and increased oxidative damage in euthymic patients with bipolar disorder. Psychiatry Clin Neurosci 68(7):551–557. doi:10.1111/pcn.12163
Clark L, Iversen SD, Goodwin GM (2002) Sustained attention deficit in bipolar disorder. Br J Psychiatry 180:313–319
Cosci F, Fava GA (2013) Staging of mental disorders: systematic review. Psychother Psychosom 82(1):20–34. doi:10.1159/000342243
Cunha AB, Andreazza AC, Gomes FA, Frey BN, da Silveira LE, Goncalves CA, Kapczinski F (2008) Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. Eur Arch Psychiatry Clin Neurosci 258(5):300–304. doi:10.1007/s00406-007-0797-0
Denicoff KD, Ali SO, Mirsky AF, Smith-Jackson EE, Leverich GS, Duncan CC, Connell EG, Post RM (1999) Relationship between prior course of illness and neuropsychological functioning in patients with bipolar disorder. J Affect Disord 56(1):67–73, S0165-0327(99)00028-2 [pii]
Duffy A, Alda M, Hajek T, Sherry SB, Grof P (2010) Early stages in the development of bipolar disorder. J Affect Disord 121(1–2):127–135. doi:10.1016/j.jad.2009.05.022
El-Badri SM, Ashton CH, Moore PB, Marsh VR, Ferrier IN (2001) Electrophysiological and cognitive function in young euthymic patients with bipolar affective disorder. Bipolar Disord 3(2):79–87
Fava GA (1999) Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications. Psychol Med 29(1):47–61
Fava GA, Kellner R (1993) Staging: a neglected dimension in psychiatric classification. Acta Psychiatr Scand 87(4):225–230
Fernandes BS, Gama CS, Cereser KM, Yatham LN, Fries GR, Colpo G, de Lucena D, Kunz M, Gomes FA, Kapczinski F (2011) Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res 45(8):995–1004. doi:10.1016/j.jpsychires.2011.03.002
Fountoulakis KN (2009) An update of evidence-based treatment of bipolar depression: where do we stand? Curr Opin Psychiatry 23(1):19–24. doi:10.1097/YCO.0b013e328333e132

Fountoulakis KN (2012) Refractoriness in bipolar disorder: definitions and evidence-based treatment. CNS Neurosci Ther 18(3):227–237. doi:10.1111/j.1755-5949.2011.00259.x

Fountoulakis KN, Vieta E (2008) Treatment of bipolar disorder: a systematic review of available data and clinical perspectives. Int J Neuropsychopharmacol 11(7):999–1029. doi:10.1017/S1461145708009231, S1461145708009231 [pii]

Fountoulakis KN, Giannakopoulos P, Kovari E, Bouras C (2008a) Assessing the role of cingulate cortex in bipolar disorder: neuropathological, structural and functional imaging data. Brain Res Rev 59(1):9–21. doi:10.1016/j.brainresrev.2008.04.005

Fountoulakis KN, Grunze H, Panagiotidis P, Kaprinis G (2008b) Treatment of bipolar depression: an update. J Affect Disord 109(1-2):21–34. doi:10.1016/j.jad.2007.10.016, S0165-0327(07)00378-3 [pii]

Fountoulakis KN, Vieta E, Bouras C, Notaridis G, Giannakopoulos P, Kaprinis G, Akiskal H (2008c) A systematic review of existing data on long-term lithium therapy: neuroprotective or neurotoxic? Int J Neuropsychopharmacol 11(2):269–287. doi:10.1017/S1461145707007821

Fountoulakis KN, Kelsoe JR, Akiskal H (2011) Receptor targets for antidepressant therapy in bipolar disorder: an overview. J Affect Disord 138(3):222–238. doi:10.1016/j.jad.2011.04.043, S0165-0327(11)00210-2 [pii]

Frank E, Nimgaonkar VL, Phillips ML, Kupfer DJ (2014) All the world's a (clinical) stage: rethinking bipolar disorder from a longitudinal perspective. Mol Psychiatry. doi:10.1038/mp.2014.71

Fries GR, Pfaffenseller B, Stertz L, Paz AV, Dargel AA, Kunz M, Kapczinski F (2012) Staging and neuroprogression in bipolar disorder. Curr Psychiatry Rep 14(6):667–675. doi:10.1007/s11920-012-0319-2

Garcia-Lopez A, De Dios-Perrino C, Ezquiaga E (2009) Polarity of the first episode and predominant polarity in a cohort of bipolar outpatients. Eur Neuropsychopharmacol 19:S571

Gelenberg AJ, Kane JM, Keller MB, Lavori P, Rosenbaum JF, Cole K, Lavelle J (1989) Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med 321(22):1489–1493. doi:10.1056/NEJM198911303212201

Goodwin F, Jamison K (2007) Manic-depressive illness, 2nd edn. Oxford University Press, New York

Grande I, Magalhaes PV, Chendo I, Stertz L, Panizutti B, Colpo GD, Rosa AR, Gama CS, Kapczinski F, Vieta E (2014) Staging bipolar disorder: clinical, biochemical, and functional correlates. Acta Psychiatr Scand 129(6):437–444. doi:10.1111/acps.12268

Hamilton BA, Naismith SL, Scott EM, Purcell S, Hickie IB (2011) Disability is already pronounced in young people with early stages of affective disorders: data from an early intervention service. J Affect Disord 131(1–3):84–91. doi:10.1016/j.jad.2010.10.052

Helms PM, Smith RE (1983) Recurrent psychotic depression. Evidence of diagnostic stability. J Affect Disord 5(1):51–54

Hickie IB, Scott J, Hermens DF, Scott EM, Naismith SL, Guastella AJ, Glozier N, McGorry PD (2013) Clinical classification in mental health at the cross-roads: which direction next? BMC Med 11:125. doi:10.1186/1741-7015-11-125

Insel TR (2010) Rethinking schizophrenia. Nature 468(7321):187–193. doi:10.1038/nature09552

Javadapour A, Malhi GS, Ivanovski B, Chen X, Wen W, Sachdev P (2007) Increased anterior cingulate cortex volume in bipolar I disorder. Aust N Z J Psychiatry 41(11):910–916. doi:10.1080/00048670701634978

Judd LL, Akiskal HS (2003) The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. J Affect Disord 73(1–2):123–131

Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 59(6):530–537, yoa20425 [pii]

Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, Solomon DA, Leon AC, Keller MB (2003) A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 60(3):261–269, yoa20225 [pii]

Judd LL, Schettler PJ, Akiskal HS, Coryell W, Leon AC, Maser JD, Solomon DA (2008) Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. Arch Gen Psychiatry 65(4):386–394. doi:10.1001/archpsyc.65.4.386, 65/4/386 [pii]

Juster RP, McEwen BS, Lupien SJ (2010) Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev 35(1):2–16. doi:10.1016/j.neubiorev.2009.10.002

Kapczinski F, Frey BN, Andreazza AC, Kauer-Sant'Anna M, Cunha AB, Post RM (2008a) Increased oxidative stress as a mechanism for decreased BDNF levels in acute manic episodes. Rev Bras Psiquiatr 30(3):243–245

Kapczinski F, Vieta E, Andreazza AC, Frey BN, Gomes FA, Tramontina J, Kauer-Sant'anna M, Grassi-Oliveira R, Post RM (2008b) Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci Biobehav Rev 32(4):675–692. doi:10.1016/j.neubiorev.2007.10.005

Kapczinski F, Dias VV, Kauer-Sant'Anna M, Brietzke E, Vazquez GH, Vieta E, Berk M (2009a) The potential use of biomarkers as an adjunctive tool for staging bipolar disorder. Prog Neuro-Psychopharmacol Biol Psychiatry 33(8):1366–1371. doi:10.1016/j.pnpbp.2009.07.027

Kapczinski F, Dias VV, Kauer-Sant'Anna M, Frey BN, Grassi-Oliveira R, Colom F, Berk M (2009b) Clinical implications of a staging model for bipolar disorders. Expert Rev Neurother 9(7):957–966. doi:10.1586/ern.09.31

Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PV, Kauer-Sant'Anna M, Klamt F, Pasquali MA, Quevedo J, Gama CS, Post R (2010) A systemic toxicity index developed to assess peripheral changes in mood episodes. Mol Psychiatry 15(8):784–786. doi:10.1038/mp.2009.112

Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PV, Kauer-Sant'Anna M, Klamt F, Moreira JC, de Bittencourt Pasquali MA, Fries GR, Quevedo J, Gama CS, Post R (2011) Peripheral biomarkers and illness activity in bipolar disorder. J Psychiatr Res 45(2):156–161. doi:10.1016/j.jpsychires.2010.05.015

Kapczinski F, Magalhaes PV, Balanza-Martinez V, Dias VV, Frangou S, Gama CS, Gonzalez-Pinto A, Grande I, Ha K, Kauer-Sant'Anna M, Kunz M, Kupka R, Leboyer M, Lopez-Jaramillo C, Post RM, Rybakowski JK, Scott J, Strejilevitch S, Tohen M, Vazquez G, Yatham L, Vieta E, Berk M (2014) Staging systems in bipolar disorder: an International Society for Bipolar Disorders Task Force report. Acta Psychiatrica Scand. doi:10.1111/acps.12305

Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, Yatham LN (2009) Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int J Neuropsychopharmacol 12(4):447–458. doi:10.1017/S1461145708009310

Kendler KS, Thornton LM, Gardner CO (2000) Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. Am J Psychiatry 157(8):1243–1251

Ketter TA, Houston JP, Adams DH, Risser RC, Meyers AL, Williamson DJ, Tohen M (2006) Differential efficacy of olanzapine and lithium in preventing manic or mixed recurrence in patients with bipolar I disorder based on number of previous manic or mixed episodes. J Clin Psychiatry 67(1):95–101

Lagopoulos J, Hermens DF, Naismith SL, Scott EM, Hickie IB (2012) Frontal lobe changes occur early in the course of affective disorders in young people. BMC Psychiatry 12:4. doi:10.1186/1471-244X-12-4

Lebowitz BK, Shear PK, Steed MA, Strakowski SM (2001) Verbal fluency in mania: relationship to number of manic episodes. Neuropsychiatr Neuropsychol Behav Neurol 14(3):177–182

Lewandowski KE, Cohen BM, Ongur D (2011) Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. Psychol Med 41(2):225–241. doi:10.1017/S0033291710001042, S0033291710001042 [pii]

Lim CS, Baldessarini RJ, Vieta E, Yucel M, Bora E, Sim K (2013) Longitudinal neuroimaging and neuropsychological changes in bipolar disorder patients: review of the evidence. Neurosci Biobehav Rev 37(3):418–435. doi:10.1016/j.neubiorev.2013.01.003

Lin A, Reniers RL, Wood SJ (2013) Clinical staging in severe mental disorder: evidence from neurocognition and neuroimaging. Br J Psychiatry Suppl 54:s11–s17. doi:10.1192/bjp.bp.112.119156

Lopez-Jaramillo C, Lopera-Vasquez J, Gallo A, Ospina-Duque J, Bell V, Torrent C, Martinez-Aran A, Vieta E (2010) Effects of recurrence on the cognitive performance of patients with bipolar I disorder: implications for relapse prevention and treatment adherence. Bipolar Disord 12(5):557–567. doi:10.1111/j.1399-5618.2010.00835.x

Magalhaes PV, Jansen K, Pinheiro RT, Klamt F, Teixeira AL, da Silva RA, Kapczinski F (2011) Systemic toxicity in early-stage mood disorders. J Psychiatr Res 45(10):1407–1409. doi:10.1016/j.jpsychires.2011.05.008

Magalhaes PV, Dodd S, Nierenberg AA, Berk M (2012a) Cumulative morbidity and prognostic staging of illness in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Aust N Z J Psychiatry 46(11):1058–1067. doi:10.1177/0004867412460593

Magalhaes PV, Jansen K, Pinheiro RT, Colpo GD, da Motta LL, Klamt F, da Silva RA, Kapczinski F (2012b) Peripheral oxidative damage in early-stage mood disorders: a nested population-based case-control study. Int J Neuropsychopharmacol 15(8):1043–1050. doi:10.1017/S1461145711001532

McGorry PD (2007) Issues for DSM-V: clinical staging: a heuristic pathway to valid nosology and safer, more effective treatment in psychiatry. Am J Psychiatry 164(6):859–860. doi:10.1176/appi.ajp.164.6.859

McGorry PD (2010a) Risk syndromes, clinical staging and DSM V: new diagnostic infrastructure for early intervention in psychiatry. Schizophr Res 120(1–3):49–53. doi:10.1016/j.schres.2010.03.016

McGorry PD (2010b) Staging in neuropsychiatry: a heuristic model for understanding, prevention and treatment. Neurotox Res 18(3–4):244–255. doi:10.1007/s12640-010-9179-x

McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ (2006) Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Aust N Z J Psychiatry 40(8):616–622. doi:10.1111/j.1440-1614.2006.01860.x

McGorry PD, Purcell R, Hickie IB, Yung AR, Pantelis C, Jackson HJ (2007) Clinical staging: a heuristic model for psychiatry and youth mental health. Med J Aust 187(7 Suppl):S40–S42

McGorry PD, Killackey E, Yung A (2008) Early intervention in psychosis: concepts, evidence and future directions. World Psychiatry 7(3):148–156

McGorry PD, Nelson B, Goldstone S, Yung AR (2010) Clinical staging: a heuristic and practical strategy for new research and better health and social outcomes for psychotic and related mood disorders. Can J Psychiatry 55(8):486–497

McIntyre RS, Correll C (2014) Predicting and preventing bipolar disorder: the need to fundamentally advance the strategic approach. Bipolar Disord 16(5):451–454. doi:10.1111/bdi.12216

McNamara RK, Nandagopal JJ, Strakowski SM, DelBello MP (2010) Preventative strategies for early-onset bipolar disorder: towards a clinical staging model. CNS Drugs 24(12):983–996. doi:10.2165/11539700-000000000-00000

Moore PB, Shepherd DJ, Eccleston D, Macmillan IC, Goswami U, McAllister VL, Ferrier IN (2001) Cerebral white matter lesions in bipolar affective disorder: relationship to outcome. Br J Psychiatry 178:172–176

Moorhead TW, McKirdy J, Sussmann JE, Hall J, Lawrie SM, Johnstone EC, McIntosh AM (2007) Progressive gray matter loss in patients with bipolar disorder. Biol Psychiatry 62(8):894–900. doi:10.1016/j.biopsych.2007.03.005

Munkholm K, Poulsen HE, Kessing LV, Vinberg M (2014) Elevated levels of urinary markers of oxidatively generated DNA and RNA damage in bipolar disorder. Bipolar Disord. doi:10.1111/bdi.12245

Nelson WH, Khan A, Orr WW Jr (1984) Delusional depression. Phenomenology, neuroendocrine function, and tricyclic antidepressant response. J Affect Disord 6(3–4):297–306

Nery FG, Chen HH, Hatch JP, Nicoletti MA, Brambilla P, Sassi RB, Mallinger AG, Keshavan MS, Soares JC (2009) Orbitofrontal cortex gray matter volumes in bipolar disorder patients: a region-of-interest MRI study. Bipolar Disord 11(2):145–153. doi:10.1111/j.1399-5618.2009.00662.x

Perry A, Tarrier N, Morriss R, McCarthy E, Limb K (1999) Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. BMJ 318(7177):149–153

Popovic D, Vieta E (2013) Clinical implications of polarity index of drugs in maintenance treatment of bipolar disorder: a naturalistic study. Eur Neuropsychopharmacol 23:S68–S69

Post RM (1992) Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 149(8):999–1010

Post RM (2010) Mechanisms of illness progression in the recurrent affective disorders. Neurotox Res 18(3–4):256–271. doi:10.1007/s12640-010-9182-2

Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, Rush AJ, Keck PE Jr, McElroy SL, Luckenbaugh DA, Pollio C, Kupka R, Nolen WA (2003) Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatry 64(6):680–690; quiz 738–789

Post RM, Altshuler LL, Frye MA, Suppes T, Keck PE Jr, McElroy SL, Leverich GS, Luckenbaugh DA, Rowe M, Pizzarello S, Kupka RW, Grunze H, Nolen WA (2010) Complexity of pharmacologic treatment required for sustained improvement in outpatients with bipolar disorder. J Clin Psychiatry 71(9):1176–1186. doi:10.4088/JCP.08m04811yel; quiz 1252–1273

Post RM, Fleming J, Kapczinski F (2012) Neurobiological correlates of illness progression in the recurrent affective disorders. J Psychiatr Res 46(5):561–573. doi:10.1016/j.jpsychires.2012.02.004

Ranjekar PK, Hinge A, Hegde MV, Ghate M, Kale A, Sitasawad S, Wagh UV, Debsikdar VB, Mahadik SP (2003) Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. Psychiatry Res 121(2):109–122

Reinares M, Colom F, Rosa AR, Bonnin CM, Franco C, Sole B, Kapczinski F, Vieta E (2010) The impact of staging bipolar disorder on treatment outcome of family psychoeducation. J Affect Disord 123(1–3):81–86. doi:10.1016/j.jad.2009.09.009

Reinares M, Papachristou E, Harvey P, Mar Bonnin C, Sanchez-Moreno J, Torrent C, Ayuso-Mateos JL, Ploubidis GB, Vieta E, Frangou S (2013) Towards a clinical staging for bipolar disorder: defining patient subtypes based on functional outcome. J Affect Disord 144(1–2):65–71. doi:10.1016/j.jad.2012.06.005

Robinson LJ, Ferrier IN (2006) Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disord 8(2):103–116. doi:10.1111/j.1399-5618.2006.00277.x, BDI277 [pii]

Rosa AR, Frey BN, Andreazza AC, Cereser KM, Cunha AB, Quevedo J, Santin A, Gottfried C, Goncalves CA, Vieta E, Kapczinski F (2006) Increased serum glial cell line-derived neurotrophic factor immunocontent during manic and depressive episodes in individuals with bipolar disorder. Neurosci Lett 407(2):146–150. doi:10.1016/j.neulet.2006.08.026

Rosa AR, Gonzalez-Ortega I, Gonzalez-Pinto A, Echeburua E, Comes M, Martinez-Aran A, Ugarte A, Fernandez M, Vieta E (2012) One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder. Acta Psychiatr Scand 125(4):335–341. doi:10.1111/j.1600-0447.2011.01830.x

Rosa AR, Magalhaes PV, Czepielewski L, Sulzbach MV, Goi PD, Vieta E, Gama CS, Kapczinski F (2014) Clinical staging in bipolar disorder: focus on cognition and functioning. J Clin Psychiatry 75(5):e450–e456. doi:10.4088/JCP.13m08625

Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, Abbott R, Hayhurst H (2006) Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. Br J Psychiatry 188:313–320. doi:10.1192/bjp.188.4.313

Scott J, Leboyer M, Hickie I, Berk M, Kapczinski F, Frank E, Kupfer D, McGorry P (2013) Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value. Br J Psychiatry 202(4):243–245. doi:10.1192/bjp.bp.112.110858

Segal ZV, Williams JM, Teasdale JD, Gemar M (1996) A cognitive science perspective on kindling and episode sensitization in recurrent affective disorder. Psychol Med 26(2):371–380

Silverstone T, McPherson H, Li Q, Doyle T (2003) Deep white matter hyperintensities in patients with bipolar depression, unipolar depression and age-matched control subjects. Bipolar Disord 5(1):53–57

Simon NM, Smoller JW, McNamara KL, Maser RS, Zalta AK, Pollack MH, Nierenberg AA, Fava M, Wong KK (2006) Telomere shortening and mood disorders: preliminary support for a

chronic stress model of accelerated aging. Biol Psychiatry 60(5):432–435. doi:10.1016/j.biopsych.2006.02.004

Soares JC, Kochunov P, Monkul ES, Nicoletti MA, Brambilla P, Sassi RB, Mallinger AG, Frank E, Kupfer DJ, Lancaster J, Fox P (2005) Structural brain changes in bipolar disorder using deformation field morphometry. Neuroreport 16(6):541–544

Strakowski SM, Wilson DR, Tohen M, Woods BT, Douglass AW, Stoll AL (1993) Structural brain abnormalities in first-episode mania. Biol Psychiatry 33(8–9):602–609

Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, Shear P, Adler CM (2002) Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. Am J Psychiatry 159(11):1841–1847

Strejilevich SA, Martino DJ (2013) Cognitive function in adulthood and elderly euthymic bipolar patients: a comparison to test models of cognitive evolution. J Affect Disord 150(3):1188–1191. doi:10.1016/j.jad.2013.05.012

Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD (1999) Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. Am J Psychiatry 156(8):1264–1266

Tohen M, Vieta E, Gonzalez-Pinto A, Reed C, Lin D, European Mania in Bipolar Longitudinal Evaluation of Medication Advisory B (2010) Baseline characteristics and outcomes in patients with first episode or multiple episodes of acute mania. J Clin Psychiatry 71(3):255–261. doi:10.4088/JCP.08m04580

Torrent C, Bonnin Cdel M, Martinez-Aran A, Valle J, Amann BL, Gonzalez-Pinto A, Crespo JM, Ibanez A, Garcia-Portilla MP, Tabares-Seisdedos R, Arango C, Colom F, Sole B, Pacchiarotti I, Rosa AR, Ayuso-Mateos JL, Anaya C, Fernandez P, Landin-Romero R, Alonso-Lana S, Ortiz-Gil J, Segura B, Barbeito S, Vega P, Fernandez M, Ugarte A, Subira M, Cerrillo E, Custal N, Menchon JM, Saiz-Ruiz J, Rodao JM, Isella S, Alegria A, Al-Halabi S, Bobes J, Galvan G, Saiz PA, Balanza-Martinez V, Selva G, Fuentes-Dura I, Correa P, Mayoral M, Chiclana G, Merchan-Naranjo J, Rapado-Castro M, Salamero M, Vieta E (2013) Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. Am J Psychiatry 170(8):852–859. doi:10.1176/appi.ajp.2012.12070971

Torres IJ, DeFreitas VG, DeFreitas CM, Kauer-Sant'Anna M, Bond DJ, Honer WG, Lam RW, Yatham LN (2010) Neurocognitive functioning in patients with bipolar I disorder recently recovered from a first manic episode. J Clin Psychiatry 71(9):1234–1242. doi:10.4088/JCP.08m04997yel

Vieta E, Reinares M, Rosa AR (2011) Staging bipolar disorder. Neurotox Res 19(2):279–285. doi:10.1007/s12640-010-9197-8

Vieta E, Popovic D, Rosa AR, Sole B, Grande I, Frey BN, Martinez-Aran A, Sanchez-Moreno J, Balanza-Martinez V, Tabares-Seisdedos R, Kapczinski F (2013) The clinical implications of cognitive impairment and allostatic load in bipolar disorder. E Psychiatry 28(1):21–29. doi:10.1016/j.eurpsy.2011.11.007

Vita A, De Peri L, Sacchetti E (2009) Gray matter, white matter, brain, and intracranial volumes in first-episode bipolar disorder: a meta-analysis of magnetic resonance imaging studies. Bipolar Disord 11(8):807–814. doi:10.1111/j.1399-5618.2009.00759.x

Walz JC, Andreazza AC, Frey BN, Cacilhas AA, Cereser KM, Cunha AB, Weyne F, Stertz L, Santin A, Goncalves CA, Kapczinski F (2007) Serum neurotrophin-3 is increased during manic and depressive episodes in bipolar disorder. Neurosci Lett 415(1):87–89. doi:10.1016/j.neulet.2007.01.002

Walz JC, Magalhaes PV, Giglio LM, Cunha AB, Stertz L, Fries GR, Andreazza AC, Kapczinski F (2009) Increased serum neurotrophin-4/5 levels in bipolar disorder. J Psychiatr Res 43(7):721–723. doi:10.1016/j.jpsychires.2008.10.005

Yatham LN, Kapczinski F, Andreazza AC, Trevor Young L, Lam RW, Kauer-Sant'anna M (2009) Accelerated age-related decrease in brain-derived neurotrophic factor levels in bipolar disorder. Int J Neuropsychopharmacol 12(1):137–139. doi:10.1017/S1461145708009449

Yung AR, McGorry PD (1996) The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull 22(2):353–370

Yung AR, McGorry PD (2007) Prediction of psychosis: setting the stage. Br J Psychiatry Suppl 51:s1–s8. doi:10.1192/bjp.191.51.s1

Zubieta JK, Huguelet P, O'Neil RL, Giordani BJ (2001) Cognitive function in euthymic bipolar I disorder. Psychiatry Res 102(1):9–20, S0165-1781(01)00242-6 [pii]