Reconsideration of bipolar disorder as a developmental disorder: importance of the time of onset.

Pierre Alexis Geoffroy, Bruno Etain, Jan Scott, Chantal Henry, Stéphane Jamain, Marion Leboyer, Frank Bellivier

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Pierre Alexis Geoffroy [a,c,d*], Bruno Etain [a,c,e], Jan Scott [b,f], Chantal Henry [a,b,c,e], Stéphane Jamain [a,d], Marion Leboyer [a,b,c,e], Frank Bellivier [a,b,c,e].

[a] INSERM, U955, Créteil, 94000, France

[b] Université Paris Est, Faculté de médecine, Créteil, 94000, France

[c] AP-HP, Hôpital H. Mondor - A. Chenevier, Pôle de Psychiatrie, Créteil, 94000, France

[d] Pôle de psychiatrie, Univ Lille Nord de France, CHRU de Lille, F-59000 Lille, France

[e] Fondation FondaMental, Créteil, 94000, France

[f]Academic Psychiatry, Institute of Neuroscience, Newcastle University, UK

*** Corresponding author**:

Pierre Alexis GEOFFROY

Pôle de Psychiatrie (Pr Leboyer)

Hôpital Albert Chenevier, Centre Expert Bipolaire,

40, rue de Mesly

94000 Créteil Cedex - FRANCE

Tel: + 33 1 49 81 32 90 - Fax: + 33 1 49 81 30 99

E-mail: pierre.a.geoffroy@gmail.com

Highlights

- BD is a heterogeneous psychiatric disorder with developmental and progressive neurophysiological alterations
- Age at onset defines homogeneous subgroups of patients with BD
- A threshold of 21 years or younger defines an early-onset BD subgroup (EOBD)
- Nearly half of all BD cases (45%) can be categorized as EOBD
- EOBD requires focused medication and targeted prevention strategies

Abstract

Bipolar disorder is a multifactorial psychiatric disorder with developmental and progressive neurophysiological alterations. This disorder is typically characterized by cyclical and recurrent episodes of mania and depression but is heterogeneous in its clinical presentation and outcome. Although the DSM-IV-TR criteria identify several features that are of phenomenological relevance, these are of less utility for defining homogeneous subgroups, for analyses of correlations with biomarkers or for directing focused medication strategies. We provide a comprehensive review of existing evidence regarding to age at onset in bipolar disorder. Eight admixture studies demonstrate three homogeneous subgroups of patients with bipolar disorder identified according to age at onset (early, intermediate and late age at onset), with two cutoff points, at 21 and 34 years. It is suggested that the early-onset subgroup has specific clinical features and outcomes different from those of the other subgroups. Early-onset subgroup may be considered a more suitable clinical phenotype for the identification of susceptibility genes with recent data demonstrating associations with genetic variants specifically in this subgroup. The use of age at onset as a specifier may also facilitate the identification of other biological markers for use in brain imaging, circadian, inflammatory and cognitive research. A key challenge is posed by the use of age at onset in treatment decision algorithms, although further research is required to increase the evidence-base. We discuss three potential benefits of specifying age at onset, namely: focused medication strategies, the targeted prevention of specific comorbid conditions and decreasing the duration of untreated illness. We argue that age at onset should be included as a specifier for bipolar disorders.

Keywords: bipolar disorder, age at onset, early-onset bipolar disorder, admixture, phenotype, genetic, biomarkers.

1. Introduction

Bipolar disorder (BD) is a major psychiatric illness typically characterized by cyclical and recurrent episodes of mania and depression that cause impairments in functioning and health-related quality of life (Rosa et al., 2008). The prevalence of the BD spectrum is about 4.4% of the population and includes the classical type I BD, defined by episodes of mania and depression, and the type II BD, with less severe hypomania and major depression (Leboyer and Kupfer, 2010). BD is the sixth cause of disability-adjusted life-years among all diseases according to the World Health Organization (Murray C and Lopez A, 1996).

Evidence suggests that individuals with BD have developmental and progressive neurophysiological alterations. BD can be considered as a developmental disorder starting early in life and resulting in pathological conditions during adulthood (Bellivier et al., in press). Patients with BD experience a chronic course of the disorder characterized by progressive cognitive impairment, residual symptoms, sleep and circadian rhythm disturbances, emotional dysregulation, and increased risk for psychiatric and medical comorbidity between mood episodes (Leboyer and Kupfer, 2010). Thus, a better understanding of onset and clinical course of BD is necessary to propose a personalized medical treatment with better prognoses.

Nosographical classifications such as the DSM-IV-TR (American Psychiatric Association, 2000) define certain specifiers of BD that have proven phenomenological relevance. However, most are of limited utility in identifying homogeneous subgroups, analyzing correlations with biological markers or guiding treatment decisions. For example, rapid cycling is a specifier, which can be relevant in clinical practice, because its presence correlates to prognosis and can guide treatment decision making (Colom and Vieta, 2009). In contrast, other specifiers have less clinical and therapeutic value; for example, the distinction

between psychotic and non-psychotic mood episodes might be better replaced by a dimensional approach to psychosis in the DSM-V classification (Henry and Etain, 2010).

The publication of the DSM-V has rekindled discussions about the most meaningful specifiers of onset, clinical course and outcome in mood disorders (Benazzi, 2009). We need to identify features that can be reliably defined, are clinically valid, that are potentially associated with biomarkers of the underlying disease process and ultimately help inform treatment decisions (Colom and Vieta, 2009). Age at onset (AAO) of BD has recently been proposed as a tool for clinical categorization. There is considerable evidence to suggest that the clinical expression of BD differs according to AAO that has therefore been identified as a potential specifier of interest (Leboyer et al., 2005 ; Colom and Vieta, 2009 ; Leboyer and Kupfer, 2010).

2. Early-onset BD as a distinct subgroup

2.1. Clinical evidence

It has been suggested that early-onset BD (EOBD) subgroup displays greater clinical homogeneity than later AAO subgroups, with specific, recurrent or more severe features, and higher levels of comorbidity with both psychiatric and somatic diseases (Leboyer M et al., 2012). For example, there are early literature reports of an association between BD with an AAO<30 years, alcoholism and sociopathy (James, 1977). Our previous literature review (Leboyer et al., 2005) indicated significant associations between EOBD and a higher frequency of psychotic symptoms, mixed episodes, comorbid anxiety, a poorer response to lithium and a higher risk of affective disorders in first-degree relatives. Perlis et al. (2004) undertook a large-scale retrospective study comparing BD patients with early-onset (age < 18 years) and patients with very early-onset (age 13-18 years). They showed, in these two

subgroups, a higher frequency of comorbid anxious and addictive disorders, thymic episode recurrence, suicide attempts, violent behavior and a shorter euthymic period, as compared to adult onset (age > 18 years) (Perlis et al., 2004). A recent review highlighted associations between EOBD and the prevalence of substance dependence (particularly alcohol, tobacco and cannabis) (Goldstein and Bukstein, 2010). Excessive cannabis use, whether occurring before or after the onset of mood symptoms, is associated with EOBD, even after adjustment for possible confounding factors (Lagerberg et al., 2011). In the USA, but less so in Europe, attention deficit hyperactivity disorder (ADHD) has also been reported to be more frequently comorbid amongst patients with EOBD (Chang, 2010).

A higher frequency of psychiatric comorbidities is not the only clinical feature associated with EOBD; this subgroup also demonstrates an increased risk for certain somatic diseases. Indeed, patients with EOBD exhibited a higher prevalence of thyroid dysfunction and cardiovascular risk factors, such as diabetes (due to glucose intolerance and insulin resistance), obesity (particularly abdominal obesity) and hypertension. The studies also noted that these cardiovascular risk factors, as well as asthma may be observed before BD diagnosis in this early-onset subgroup (Kupfer, 2005 ; McIntyre and Jerrell, 2009 ; Jerrell et al., 2010).

This overview is far from exhaustive, but demonstrates that the EOBD subgroup is consistently characterized by a higher level of comorbid psychiatric and somatic conditions. However, the definitions used to classify cases in this subgroup differ widely between studies, with some defining early onset subgroup as pediatric BD (childhood onset BD with modified diagnostic criteria or adult type BD with AAO<18 years), juvenile BD (often classified using diagnostic criteria modified from adult BD criteria) or early adult BD subtype (adult BD diagnosis but with varying AAO cutoffs ranging from 18-30 years). These definitions are often used arbitrarily and have therefore undermined the strength of empirical support for such concepts. As such, more robust and replicable evidence for the existence of an EOBD subgroup was needed. This has now been provided by admixture studies.

2.2. Evidence from admixture analyses

The AAO of BD varies considerably between patients, beginning at any age from early childhood to late adulthood. Admixture analyses are robust methodological tools that aim at modeling the distribution of AAO. The purpose of an admixture study is to demonstrate that a mixture of "n" subgroups, each following a Gaussian distribution, fits the observed distribution. In the last decade, eight admixture studies have independently demonstrated the existence of three subgroups of BD patients, defined on the basis of AAO (early, intermediate and late). So far, only one study has failed to replicate the EOBD finding, instead identifying two AAO subgroups (an early subgroup and an intermediate/late onset subgroup) (Javaid et al., 2011).

+++ Insert Table 1 here +++

As shown in Table 1, the mean (and standard deviation) AAO for the three subgroups and the percentage of patients belonging to subgroups are provided for each study (Bellivier et al., 2001; Bellivier et al., 2003 ; Hamshere et al., 2009 ; Severino et al., 2009 ; Lin et al., 2006 ; Ortiz et al., 2010 ; Tozzi et al., 2011; Bellivier et al., 2011). These characteristics have replicated in various populations (eg European and American), supporting the stability of this model. According to the published findings, an onset at the age $\leq$ 21 years can be used to define the early onset subgroup. The very small standard deviation observed for the threshold values (21.33±1.41 years) suggests that the model is highly robust. The percentage of EOBD patients is about 45% (mean percentage weighted for the number of subjects per study).

As shown in Table 2, when this consensual AAO threshold is applied, replicable evidence emerges of significant associations between EOBD and suicide attempts, rapid cycling, drug abuse, obsessive-compulsive disorder and increased familial risk for affective

disorders. Suggestive evidence has also been proposed for associations to psychotic features, alcohol abuse and panic disorder.

+++ Insert Table 2 here +++

The mixture of three AAO subgroups is observed in samples of patients with type I BD and in samples including various proportions of patients with type I and type II BD. Similar findings have been observed in pure populations of BD II disorder (Benazzi, 2004), again showing the existence of the three AAO subgroups with an early-onset subgroup with an AAO<20 years. This model of EOBD therefore appears to be valid for both type I and type II BD and represents a putative clinical indicator of BD subgroups.

3. Biomarkers in EOBD

3.1. Is EOBD a more heritable form of BD?

Our relative failure to replicate findings in psychiatric genetics may be related to difficulties in defining heritable phenotypes and to the fact that the proportional influence of genes may vary with the age at onset of a mental disorder (Cahill et al., 2009). The use of a candidate symptom approach aims to use phenotypic markers to identify more homogeneous and familial forms of diseases among affected subjects (Leboyer et al., 1998b). The use of AAO in BD is an excellent example of this strategy, with the early-onset sub-type being a more suitable clinical phenotype for the identification of susceptibility genes.

Evidence suggests that EOBD is a heritable subtype of BD as there is a higher than expected prevalence of BD in first-degree relatives of EOBD probands (age 30 years being the cutting point in this study) (Taylor and Abrams, 1981). Studies undertaken in the Amish community in the 1990s also showed that the rate of affective illness was higher among relatives of probands with early-onset bipolar I disorder (Pauls et al., 1992). Two reviews note

that the frequency of BD in the first-degree relatives of children with BD (15-42%) is higher than that in first-degree relatives of subjects with adult onset BD (8.7%) (Mick and Faraone, 2009 ; Schürhoff et al., 2000).

A segregation analysis of 177 patients with type I BD and 2407 first- and second-degree relatives suggested that the mode of genetic transmission might be less complex for the early-onset sub-type than for other later onset subtypes (Grigoroiu-Serbanescu et al., 2001). The proportion of affected first-degree relatives was significantly higher for early-onset probands (AAO < 25 years) than for the late-onset probands (AAO > 25 years) (respectively 9.4% versus 5.5%; $p = 0.01$). Furthermore, a different pattern of familial transmission as a function of the AAO was suggested: it was hypothesized that in the early-onset group, the pattern of disease transmission was consistent with a model involving a single major gene associated with a polygenic component. By contrast, in the late-onset group, disease transmission was evidently multifactorial. Although EOBD cannot be considered to be a monogenic subtype of BD, these findings suggest that the identification of genetic susceptibility factors may be favored by studies specifically performed within this subgroup. It is also argued that a smaller number of genes might be implicated in the susceptibility to EOBD, with these genes having a higher penetrance, as compared to later onset BD (Faraone et al., 2003).

Since the 1990s, research on the susceptibility genes in BD has demonstrated specific associations between genetic markers and EOBD. For example, Baron et al. (1990) demonstrated that the X-linked phenotype is a particularly severe form of BD characterized by early onset. Further evidence has been provided by candidate gene studies that hypothesized abnormalities of neurotransmission or neuronal plasticity in EOBD. Several associations have been reported with EOBD, including the apoliprotein E e4 allele (Bellivier et al., 1997), the short variant of the 5-HTTLPR polymorphism of the promoter of the gene encoding the serotonin transporter (Ospina-Duque et al., 2000), a polymorphism of the gene

encoding the brain-derived neurotrophic factor (BDNF) (Tang et al., 2008) and certain variants of the catechol-O-methyltransferase (COMT) gene (Massat et al., 2011).

Genetic linkage-based approaches have also benefited from this phenotypic refinement of BD according to AAO. We undertook a large European study of sib-pairs with EOBD and demonstrated linkage with the 2p21, 2q14.3, 3p14, 5q33, 7q36, 10q23, 16q23, and 20p12 regions (Etain et al., 2006). Further investigations focusing on the 20p12 region revealed a specific association between a variant of the promoter of the *SNAP25* gene (encoding a presynaptic plasma membrane protein essential for the triggering of vesicular fusion and neurotransmitter release) and EOBD. This variant has functional consequences since it is associated with higher levels of mRNA expression in the prefrontal region of the cortex (Etain et al., 2010). Finally, two recent whole-genome analyses of copy number variations (CNVs, resulting from deletions and duplications of chromosome regions) identified microdeletions and microduplications in certain regions that were specifically associated with EOBD (Priebe et al., 2011; Malhotra et al., 2011).

Taken as a whole, the above findings support the notion that the stratification of genetic findings according to AAO or specific sampling of EOBD probands may lead to the identification of genetic susceptibility markers that might be missed if the analyses include unselected BD populations with AAO's spanning the early, intermediate and late onset subgroups.

3.2. Are there specific brain imaging markers of EOBD?

In BD, two recent meta-analyses (one of functional neuroimaging of emotional regulation and the other of whole-brain structural imaging) demonstrated grey matter abnormalities within a cortical-cognitive brain network have been associated with the

regulation of emotions and an increased activation in ventral limbic brain regions that mediate the experience of emotions and generation of emotional responses (Houenou et al., 2011).

In studies using Magnetic Resonance Imaging (MRI), EOBD is characterized by a consistent hyperintensity of the subcortical white matter (Pillai et al., 2002), but this observation is nonspecific, being common to several other mental disorders, such as depression, schizophrenia and post-traumatic stress syndrome (Breeze et al., 2003). Young patients with BD also have smaller amygdala, hippocampus and superior temporal gyrus volumes than controls, although these findings require further replication (Blumberg et al., 2003 ; DelBello et al., 2004 ; Chen et al., 2004).

Functional MRI studies have also provided the first neuroanatomical demonstration of the potential utility of separating out the EOBD subgroup: they reveal a significantly lower sulcal index in the right dorsolateral prefrontal region and a significantly lower overall sulcal index throughout both hemispheres in the early-onset subgroup than in an intermediate-onset group and in the control group (Penttilä et al., 2009). As expected, subcortical prefrontal activation in affected children and adolescents has been described as abnormal, although no control group findings were given (Chang et al., 2004).

Magnetic resonance spectroscopy, an imaging technique providing both biochemical and molecular data, demonstrated that, compared to healthy controls, children with a mood disorder and a family history of BD present biochemical dysregulation of N-acetylaspartate and phosphocreatine in the frontal lobe and basal ganglion (Cecil et al., 2003). Using a similar approach, Patel et al. demonstrated localized abnormalities in brain metabolites (eg anterior cingulate N-acetylaspartate and ventral lateral pre-frontal cortex choline levels) in adolescents with BD depression compared with healthy controls (Patel et al., 2008). However, these studies are limited by lack of comparative data on other BD AAO subgroups, small sample sizes and the difficulty of controlling for the potential confounding effects of medication.

Electroencephalographic studies of BD have reported profound prefrontal inter-hemispheric asymmetry, with under-activation of the right side specifically being noted in young patients (Kentgen et al., 2000). No such asymmetry has been reported in middle-aged patients (Smit et al., 2007). These findings are consistent with poor functioning of the right parieto-temporal region, particularly in early-onset and severe forms of BD.

3.3. Cognitive markers and EOBD

Data specifically focusing on the cognitive profile of EOBD remains scarce. Nevertheless, Cahill et al. (2009) reported that have been undertaken have identified some abnormalities that may be specific to the AAO subgroup.

Regarding emotional cognitive functions, EOBD cases show greater reactivity to emotional stimuli (Post et al., 2001), and stronger reactions to threatening situations (Grillon et al., 2005). Compared with healthy controls, both children with BD and those with a high familial risk of BD show poorer recognition of facial emotional expressions, and this deficit seems to predict progression to BD in the at risk children (Brotman et al., 2008).

Cognitive disturbances have been reported in BD, such as attention, memory and executive functions (Sole et al., 2011). Impairments in working memory, visual-motor skills, and inhibitory control seem to be particularly marked in young BD patients when compared with healthy, age and gender-matched adolescents (Lera-Miguel et al., 2011).

Finally, a recent meta-analysis from studies of early onset schizophrenia and pediatric BD (defined as AAO<18 years), found that individuals with pediatric BD demonstrate deficits in verbal learning and memory, processing speed, and executive control. Interestingly, these deficits are quantitatively less marked but qualitatively similar to those found in patients with early onset schizophrenia (Nieto and Castellanos, 2011).

3.4. EOBD, circadian rhythms and inflammatory markers

Circadian abnormalities are common in BD (Etain et al., 2011 ; Milhiet et al., 2011) and represent potentially relevant markers of susceptibility to the disorder that may be more evident in EOBD. Sleep problems, such as insomnia, disturbed sleep/wake cycles, night to night variability in sleep quality, difficulties falling asleep and a high frequency of rapid eye movements, have been reported in euthymic BD patients (Harvey, 2008 ; Scott, 2011).

Some of these markers may be present in the early or prodromal stages of BD and/or represent endophenotypes, since they are also found in healthy children born to bipolar parents (Mansour et al., 2005 ; Grandin et al., 2006). The EOBD subgroup has also been found to have higher frequency of sleeping problems, with, in particular, problems falling asleep (Staton, 2008). A correlation between earlier age at onset and greater eveningness has also been reported (Mansour et al., 2005).

Although the published data is inconclusive, several studies have shown that inflammation marker levels are high during manic and depressive episodes (Hamdani et al., 2012). For example, in the Course and Outcome of Bipolar Youth (COBY) study, associations have been found between hypomanic/manic symptom severity and high-sensitivity C-reactive protein and IL-6 levels (Goldstein et al., 2011). However, confirmation of these findings is required and to date, a specific immune-inflammatory signature of EOBD has yet to be demonstrated.

In summary, we suggest that the relevance of a definition of EOBD relies not only on the consensus on the AAO threshold or a clinically homogenous profile. It also relies on correlations with biomarkers that may validate the existence of this subgroup. Overall, several genetic, biological, circadian, brain imaging and cognitive markers may be associated with EOBD. However, biomarkers studies use more diverse threshold values to define EOBD than

admixture studies and this represents a significant limitation for the reliability and robustness of the results. In the future, we suggest that consensual threshold AAO values derived from admixture analyses should be systematically used in biomarker studies of EOBD.

4. Early environment and EOBD

Several independent studies show intra-familial similarities in AAO in BD (James, 1977 ; Bellivier et al., 2003 ; Leboyer et al., 1998a), although this familial clustering failed to reach significance in one study (Schulze et al., 2006). Therefore, AAO could possibly be driven by genetic factors and/or shared environmental factors.

Childhood trauma is one of the environmental factors most widely studied in BD (Daruy-Filho et al., 2011 ; Post et al., 2001). Such trauma is common and frequently severe in BD (Etain et al., 2008), but has been shown to be correlated with several clinical characteristics of BD, including earlier onset (Post et al., 2001 ; Daruy-Filho et al., 2011). The frequency of obstetric complications has been shown to be higher in individuals who later develop EOBD (Guth et al., 1993). Patients with EOBD also have higher frequencies of stressful life events and a family history of psychiatric problems, whereas later-onset subtypes may be more frequently associated with vascular comorbid conditions and greater levels of support from family and friends. This suggests that EOBD may be driven in part by more frequent occurrence of early stressful events as compared with later-onset BD (Hays et al., 1998).

The AAO of BD has also been suggested to be influenced by several genetic variants in candidate genes such as DRD2 (Squassina et al., 2011), glycogen synthase kinase 3-beta (GSK3-beta) and Per3 genes (Benedetti et al., 2008). Although these studies have not been

replicated to date, this suggests the involvement of genetic variants in influencing the AAO of the disease.

5. Specificities of EOBD management

Evidence indicates that EOBD is a more severe clinical form of BD. Early intervention is essential in such cases, given the risk of chronic disease, the high incidence of recurrence and, in the absence of appropriate management, a greater likelihood of poor outcome (Chang, 2010). However, most studies have shown that the time interval from BD onset to the initiation of treatment is inversely correlated with AAO (Post et al., 2010). This shocking statistic represents one of the most replicated findings in the BD literature on factors associated with prolonged duration of untreated illness (Altamura et al., 2010). The fact that patients with EOBD experience the longest duration of untreated illness has numerous explanations. For example, EOBD is more complex in its clinical expression and is associated with greater comorbidity, increasing the risk of misdiagnosis or missed diagnosis (Post et al., 2010 ; Scott and Leboyer, 2011). However, it possibly indicates also the lack of awareness amongst clinicians of the peak age of onset of BD or their reluctance to make a diagnosis that has lifetime implications and/or may be viewed as carrying stigma for the individual.

Even if clinicians establish a diagnosis of EOBD, current clinical practice guidelines tend to include relatively nonspecific treatment algorithms focused on polarity at the time of treatment initiation, predominant polarity or clinical features such as the presence of rapid cycling (Yatham et al., 2005 ; Yatham et al., 2009). We believe that AAO is an equally useful prognostic marker of response to treatment, which should be considered for inclusion in treatment recommendations.

Three major advantages to incorporating AAO into treatment decision algorithms can be underlined: it would make specific age-appropriate treatment more possible, it would encourage the systematic screening and targeted prevention of certain comorbid conditions that frequently occur in EOBD and it would hopefully raise awareness of the existence of the EOBD subtype allowing reduced delays in diagnosis and introduction of mood stabilizers.

It has been suggested that different AAO subgroups show differential responses to some standard BD treatments. However, this notion is disputed (there is some evidence that lithium response may differ in EOBD subgroups) possibly because of the presence of more comorbidities or rapid cycling disorder or because of delayed treatment introduction (Schürhoff et al., 2000 ; Yatham et al., 2005). Berk et al. (2011) also highlighted that poor response to most mood stabilizers is found in those with a history of multiple BD episodes – who in turn had more often an EOBD. The lack of studies is however a major limitation in making evidence-based decisions on treatments for EOBD.

Current clinical guidelines suggest there is 'level 2' evidence for the use of lithium, valproate and atypical antipsychotics (APAs), with slightly less evidence for oxcarbazepine (Yatham et al., 2009). One of the few studies available — a 24 months prospective study of the long-term response to mood stabilizers in three AAO subgroups (with EOBD defined as AAO <30 years) — showed mood stabilizers to be more effective for major depression prevention in the early-onset subgroup compared to the other subgroups, whereas no difference was found in terms of prevention of manic/hypomanic and mixed episodes (Dell'osso et al., 2009). The literature is however complicated to disentangle and, for example, a recent review proposed that EOBD is actually an independent predictor of a poor response to lithium (Rohayem et al., 2008). Some evidence to support this view can be found in an earlier study conducted by Duffy et al. (2002) suggesting that, in EOBD, family history of response to lithium was the strongest predictor of current lithium response. In addition, Moore et al., using magnetic resonance spectroscopy, showed that brain lithium

concentrations were lower in children than in adults with BD — perhaps suggesting that the dose of lithium required to prevent relapse in EOBD cases may differ from later onset cases (Moore et al., 2002). However, the issue of lithium response in EOBD remains controversial, and there is a need to increase the evidence base through targeted studies in the EOBD group.

As well as the treatment of BD in early onset cases, it is important to consider the comorbid psychiatric and somatic disorders that have frequently been reported. Systematic screening for substance misuse, anxiety disorders and ADHD in this population appears to be essential for prevention, education, screening for risk factors and early intervention (Goldstein and Bukstein, 2010 ; Henry and Etain, 2010). Careful physical health monitoring, in particular concerning cardio-vascular risks, should be centrally implemented in the management of EOBD. These disorders are especially important to assess at baseline and to monitor prospectively, given the recognized side effects and adverse effects that can accompany treatment with certain APAs for example.

In summary, using AAO as a specifier might improve clinical awareness of early intervention and proactive management of EOBD. In addition, early recognition would improve the prospects for the 'primary prevention' of secondary problems such as substance misuse, suicidal behaviors and other comorbid disorders. For researchers, identifying EOBD in treatment algorithms would enable clinicians to begin to understand the most age-appropriate, as well as effective treatments for BD.

6. Conclusion

An appraisal of the published literature confirms that EOBD can be reliably defined as the onset of BD at or before the age of 21 years, a threshold reported consistently in admixture studies. The validity of this EOBD subtype is reinforced by observed associations

with genetic, cognitive, circadian, inflammatory and brain imaging potential markers, and with environmental susceptibility factors such as childhood trauma.

The existence of EOBD is important clinically as well as for basic science research. An early onset of BD is a robust and reliable marker in order to identify a clinical subtype of BD that is complex in its clinical expression, including high levels of psychiatric and somatic comorbidities, and has a less favourable course and outcome than later AAO subtypes. It is not yet clear whether these findings reflect the underlying disease process in EOBD or are a consequence of iatrogen factors, namely the late diagnosis and delay in the introduction of optimal treatment (Scott and Leboyer, 2011).

The high prevalence of early-onset forms among patients with BD (about 45%) is a potent argument for the need to raise the awareness of clinicians to the existence and specific treatment implications of EOBD. The early detection is the major challenge in the management of BD. However, we acknowledge that accurate diagnosis is by no means straightforward, as EOBD is associated with a range of polymorphous clinical presentations. When EOBD is suspected, clinicians need to consider therapeutic strategies that prevent suicidal behavior and reduce the risk for addictive and anxiety comorbidities. To improve the evidence-base for treatments of EOBD, it would be useful to systematically include an AAO specifier in clinical trials (both those performed during acute phases and long term response) in order to identify differential response profiles according to AAO.

In conclusion, due to its consensual definition, its utility for defining more clinically homogeneous subgroups and its correlation with biomarkers, early onset constitutes a potentially important specifier of BD that could be usefully integrated into future nosographical classifications. A key challenge is posed by the use of AAO in treatment decision algorithms, but further research in this area would aid clinicians in developing focused medication strategies.

References

Altamura, A. C., Buoli, M., Albano, A., and Dell'Osso, B., 2010. Age at onset and latency to treatment (duration of untreated illness) in patients with mood and anxiety disorders: a naturalistic study. Int Clin Psychopharmacol 25, 172–179.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR Fourth Edition. 4th ed. Arlington: American Psychiatric Publishing, Inc.

Baron, M., Hamburger, R., Sandkuyl, L. A., Risch, N., Mandel, B., Endicott, J., Belmaker, R. H., and Ott, J., 1990. The impact of phenotypic variation on genetic analysis: application to X-linkage in manic-depressive illness. Acta Psychiatr Scand 82, 196–203.

Bellivier, F., Etain, B., Malafosse, A., Henry, C., Kahn, J.-P., Elgrabli-Wajsbrot, O., Jamain, S., Azorin, J.-M., Frank, E., Scott, J., et al., 2011. Age at onset in bipolar I affective disorder in the USA and Europe. The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22188366 [Accessed January 14, 2012].

Bellivier, F., Geoffroy, P.A., Scott, J., Schurhoff, F., Leboyer, M., and Etain, B. (In press). Biomarkers of bipolar disorder: specific or shared with schizophrenia? Front Biosci (Elite Ed).

Bellivier, F., Golmard, J. L., Henry, C., Leboyer, M., and Schürhoff, F., 2001. Admixture analysis of age at onset in bipolar I affective disorder. Arch. Gen. Psychiatry 58, 510–512.

Bellivier, F., Golmard, J.-L., Rietschel, M., Schulze, T. G., Malafosse, A., Preisig, M., McKeon, P., Mynett-Johnson, L., Henry, C., and Leboyer, M., 2003. Age at onset in bipolar I affective disorder: further evidence for three subgroups. Am J Psychiatry 160, 999–1001.

Bellivier, F., Laplanche, J. L., Schürhoff, F., Feingold, J., Féline, A., Jouvent, R., Launay, J. M., and Leboyer, M., 1997. Apolipoprotein E gene polymorphism in early and late onset bipolar patients. Neurosci. Lett. 233, 45–48.

Benazzi, F., 2004. Age at onset of bipolar II disorder. Can J Psychiatry 49, 495–496.

Benazzi, F., 2009. Classifying mood disorders by age-at-onset instead of polarity. Prog. Neuropsychopharmacol. Biol. Psychiatry 33, 86–93.

Benedetti, F., Dallaspezia, S., Colombo, C., Pirovano, A., Marino, E., and Smeraldi, E., 2008. A length polymorphism in the circadian clock gene Per3 influences age at onset of bipolar disorder. Neurosci. Lett. 445, 184–187.

Berk, M., Brnabic, A., Dodd, S., Kelin, K., Tohen, M., Malhi, G. S., Berk, L., Conus, P., and McGorry, P. D., 2011. 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, 87–98.

Blumberg, H. P., Kaufman, J., Martin, A., Whiteman, R., Zhang, J. H., Gore, J. C., Charney, D. S., Krystal, J. H., and Peterson, B. S., 2003. Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. Arch. Gen. Psychiatry 60, 1201–1208.

Breeze, J. L., Hesdorffer, D. C., Hong, X., Frazier, J. A., and Renshaw, P. F., 2003. Clinical significance of brain white matter hyperintensities in young adults with psychiatric illness. Harv Rev Psychiatry 11, 269–283.

Brotman, M. A., Guyer, A. E., Lawson, E. S., Horsey, S. E., Rich, B. A., Dickstein, D. P., Pine, D. S., and Leibenluft, E., 2008. Facial emotion labeling deficits in children and adolescents at risk for bipolar disorder. Am J Psychiatry 165, 385–389.

Cahill, C. M., Walter, G., and Malhi, G. S., 2009. Neurocognition in bipolar disorder and juvenile bipolar disorder. J Can Acad Child Adolesc Psychiatry 18, 221–230.

Cecil, K. M., DelBello, M. P., Sellars, M. C., and Strakowski, S. M., 2003. Proton magnetic resonance spectroscopy of the frontal lobe and cerebellar vermis in children with a mood disorder and a familial risk for bipolar disorders. J Child Adolesc Psychopharmacol 13, 545–555.

Chang, K., Adleman, N. E., Dienes, K., Simeonova, D. I., Menon, V., and Reiss, A., 2004. Anomalous prefrontal-subcortical activation in familial pediatric bipolar disorder: a functional magnetic resonance imaging investigation. Arch. Gen. Psychiatry 61, 781–792.

Chang, K. D., 2010. Course and impact of bipolar disorder in young patients. J Clin Psychiatry 71, e05.

Chen, H. H., Nicoletti, M. A., Hatch, J. P., Sassi, R. B., Axelson, D., Brambilla, P., Monkul, E. S., Keshavan, M. S., Ryan, N. D., Birmaher, B., et al., 2004. Abnormal left superior temporal gyrus volumes in children and adolescents with bipolar disorder: a magnetic resonance imaging study. Neurosci. Lett 363, 65–68.

Colom, F., and Vieta, E., 2009. The road to DSM-V. Bipolar disorder episode and course specifiers. Psychopathology 42, 209–218.

Daruy-Filho, L., Brietzke, E., Lafer, B., and Grassi-Oliveira, R., 2011. Childhood maltreatment and clinical outcomes of bipolar disorder. Acta Psychiatr Scand 124, 427–434.

DelBello, M. P., Zimmerman, M. E., Mills, N. P., Getz, G. E., and Strakowski, S. M., 2004. Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. Bipolar Disord 6, 43–52.

Dell'osso, B., Buoli, M., Riundi, R., D'Urso, N., Pozzoli, S., Bassetti, R., Mundo, E., and Altamura, A. C., 2009. Clinical characteristics and long-term response to mood stabilizers in patients with bipolar disorder and different age at onset. Neuropsychiatr

Dis Treat 5, 399–404.

Duffy, A., Alda, M., Kutcher, S., Cavazzoni, P., Robertson, C., Grof, E., and Grof, P., 2002. A prospective study of the offspring of bipolar parents responsive and nonresponsive to lithium treatment. J Clin Psychiatry 63, 1171–1178.

Etain, B., Dumaine, A., Mathieu, F., Chevalier, F., Henry, C., Kahn, J.-P., Deshommes, J., Bellivier, F., Leboyer, M., and Jamain, S., 2010. A SNAP25 promoter variant is associated with early-onset bipolar disorder and a high expression level in brain. Mol. Psychiatry 15, 748–755.

Etain, B., Henry, C., Bellivier, F., Mathieu, F., and Leboyer, M., 2008. Beyond genetics: childhood affective trauma in bipolar disorder. Bipolar Disord 10, 867–876.

Etain, B., Mathieu, F., Rietschel, M., Maier, W., Albus, M., McKeon, P., Roche, S., Kealey, C., Blackwood, D., Muir, W., et al., 2006. Genome-wide scan for genes involved in bipolar affective disorder in 70 European families ascertained through a bipolar type I early-onset proband: supportive evidence for linkage at 3p14. Mol. Psychiatry 11, 685–694.

Etain, B., Milhiet, V., Bellivier, F., and Leboyer, M. 2011. Genetics of circadian rhythms and mood spectrum disorders. Eur Neuropsychopharmacol 21 Suppl 4, S676–682.

Faraone, S. V., Glatt, S. J., and Tsuang, M. T., 2003. The genetics of pediatric-onset bipolar disorder. Biol. Psychiatry 53, 970–977.

Goldstein, B. I., and Bukstein, O. G., 2010. Comorbid substance use disorders among youth with bipolar disorder: opportunities for early identification and prevention. J Clin Psychiatry 71, 348–358.

Goldstein, B. I., Collinger, K. A., Lotrich, F., Marsland, A. L., Gill, M.-K., Axelson, D. A., and Birmaher, B., 2011. Preliminary findings regarding proinflammatory markers and brain-derived neurotrophic factor among adolescents with bipolar spectrum disorders. J Child Adolesc Psychopharmacol 21, 479–484.

Grandin, L. D., Alloy, L. B., and Abramson, L. Y., 2006. The social zeitgeber theory, circadian rhythms, and mood disorders: review and evaluation. Clin Psychol Rev 26, 679–694.

Grigoroiu-Serbanescu, M., Martinez, M., Nöthen, M. M., Grinberg, M., Sima, D., Propping, P., Marinescu, E., and Hrestic, M., 2001. Different familial transmission patterns in bipolar I disorder with onset before and after age 25. Am. J. Med. Genet 105, 765–773.

Grillon, C., Warner, V., Hille, J., Merikangas, K. R., Bruder, G. E., Tenke, C. E., Nomura, Y., Leite, P., and Weissman, M. M., 2005. Families at high and low risk for depression: a three-generation startle study. Biol. Psychiatry 57, 953–960.

Guth, C., Jones, P., and Murray, R., 1993. Familial psychiatric illness and obstetric complications in early-onset affective disorder. A case-control study. Br J Psychiatry

163, 492–498.

Hamdani, N., Tamouza, R., and Leboyer, M., 2012. Immuno- inflammatory markers of bipolar disorder: a review of evidence. Front Biosci (Elite Ed) 4, 2170–2182.

Hamshere, M. L., Gordon-Smith, K., Forty, L., Jones, L., Caesar, S., Fraser, C., Hyde, S., Tredget, J., Kirov, G., Jones, I., et al., 2009. Age-at-onset in bipolar-I disorder: mixture analysis of 1369 cases identifies three distinct clinical sub-groups. J Affect Disord 116, 23–29.

Harvey, A. G., 2008. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. Am J Psychiatry 165, 820–829.

Hays, J. C., Krishnan, K. R., George, L. K., and Blazer, D. G., 1998. Age of first onset of bipolar disorder: demographic, family history, and psychosocial correlates. Depress Anxiety 7, 76–82.

Henry, C., and Etain, B., 2010. New ways to classify bipolar disorders: going from categorical groups to symptom clusters or dimensions. Curr Psychiatry Rep 12, 505–511.

Houenou, J., Frommberger, J., Carde, S., Glasbrenner, M., Diener, C., Leboyer, M., and Wessa, M., 2011. Neuroimaging-based markers of bipolar disorder: Evidence from two meta-analyses. J Affect Disord. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21470688 [Accessed June 8, 2011].

James, N. M., 1977. Early- and late-onset bipolar affective disorder. A genetic study. Arch. Gen. Psychiatry 34, 715–717.

Javaid, N., Kennedy, J. L., and De Luca, V., 2011. Ethnicity and Age at Onset in Bipolar Spectrum Disorders. CNS Spectr. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21632013 [Accessed June 9, 2011].

Jerrell, J. M., McIntyre, R. S., and Tripathi, A., 2010. A cohort study of the prevalence and impact of comorbid medical conditions in pediatric bipolar disorder. J Clin Psychiatry 71, 1518–1525.

Kentgen, L. M., Tenke, C. E., Pine, D. S., Fong, R., Klein, R. G., and Bruder, G. E., 2000. Electroencephalographic asymmetries in adolescents with major depression: influence of comorbidity with anxiety disorders. J Abnorm Psychol 109, 797–802.

Kupfer, D. J., 2005. The increasing medical burden in bipolar disorder. JAMA 293, 2528–2530.

Lagerberg, T. V., Sundet, K., Aminoff, S. R., Berg, A. O., Ringen, P. A., Andreassen, O. A., and Melle, I., 2011. Excessive cannabis use is associated with earlier age at onset in bipolar disorder. Eur Arch Psychiatry Clin Neurosci. Available at: http://www.ncbi.nlm.nih.gov.gate2.inist.fr/pubmed/21267743 [Accessed March 7, 2011].

Leboyer M, Soreca I, Scott J, Frye M, Henry C, Kupfer DJ, 2012. Bipolar Disorder: A multi-systemic inflammatory disease ? J Affect Disord. Available at: (accepted).

Leboyer, M., Bellivier, F., McKeon, P., Albus, M., Borrman, M., Perez-Diaz, F., Mynett-Johnson, L., Feingold, J., and Maier, W., 1998a. Age at onset and gender resemblance in bipolar siblings. Psychiatry Res 81, 125–131.

Leboyer, M., Bellivier, F., Nosten-Bertrand, M., Jouvent, R., Pauls, D., and Mallet, J., 1998b. Psychiatric genetics: search for phenotypes. Trends Neurosci 21, 102–105.

Leboyer, M., Henry, C., Paillere-Martinot, M.-L., and Bellivier, F., 2005. Age at onset in bipolar affective disorders: a review. Bipolar Disord 7, 111–118.

Leboyer, M., and Kupfer, D. J., 2010. Bipolar disorder: new perspectives in health care and prevention. J Clin Psychiatry 71, 1689–1695.

Lera-Miguel, S., Andrés-Perpiñá, S., Calvo, R., Fatjó-Vilas, M., Lourdes, F., and Lázaro, L., 2011. Early-onset bipolar disorder: how about visual-spatial skills and executive functions? Eur Arch Psychiatry Clin Neurosci 261, 195–203.

Lin, P.-I., McInnis, M. G., Potash, J. B., Willour, V., MacKinnon, D. F., DePaulo, J. R., and Zandi, P. P., 2006. Clinical correlates and familial aggregation of age at onset in bipolar disorder. Am J Psychiatry 163, 240–246.

Malhotra, D., McCarthy, S., Michaelson, J. J., Vacic, V., Burdick, K. E., Yoon, S., Cichon, S., Corvin, A., Gary, S., Gershon, E. S., et al., 2011. High Frequencies of De Novo CNVs in Bipolar Disorder and Schizophrenia. Neuron 72, 951–963.

Mansour, H. A., Monk, T. H., and Nimgaonkar, V. L., 2005. Circadian genes and bipolar disorder. Ann. Med 37, 196–205.

Massat, I., Kocabas, N. A., Crisafulli, C., Chiesa, A., Calati, R., Linotte, S., Kasper, S., Fink, M., Antonijevic, I., Forray, C., et al., 2011. COMT and age at onset in mood disorders: A replication and extension study. Neurosci Lett. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21600957 [Accessed June 8, 2011].

McIntyre, R. S., and Jerrell, J. M., 2009. Polypharmacy in children and adolescents treated for major depressive disorder: a claims database study. J Clin Psychiatry 70, 240–246.

Mick, E., and Faraone, S. V., 2009. Family and genetic association studies of bipolar disorder in children. Child Adolesc Psychiatr Clin N Am 18, 441–453, x.

Milhiet, V., Etain, B., Boudebesse, C., and Bellivier, F. (2011). Circadian biomarkers, circadian genes and bipolar disorders. Journal of Physiology, Paris. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21767641 [Accessed September 24, 2011].

Moore, C. M., Demopulos, C. M., Henry, M. E., Steingard, R. J., Zamvil, L., Katic, A., Breeze, J. L., Moore, J. C., Cohen, B. M., and Renshaw, P. F., 2002. Brain-to-serum lithium ratio and age: an in vivo magnetic resonance spectroscopy study. Am J

Psychiatry 159, 1240–1242.

Murray C, Lopez A The Global Burden of Disease. A Comprehensive Assessment of Morbidity and Disability From Diseases, Injuries and Risk Factors in 1990 and Projected to 2020. Cambridge, Massachusetts: Harvard University Press; 1996.

Nieto, R. G., and Castellanos, F. X., 2011. A meta-analysis of neuropsychological functioning in patients with early onset schizophrenia and pediatric bipolar disorder. J Clin Child Adolesc Psychol 40, 266–280.

Ortiz, A., Bradler, K., Slaney, C., Garnham, J., Ruzickova, M., O'Donovan, C., Hajek, T., and Alda, M., 2010. An admixture analysis of the age at index episodes in bipolar disorder. Psychiatry Res. Available at: http://www.ncbi.nlm.nih.gov.gate2.inist.fr/pubmed/21131056 [Accessed March 8, 2011].

Ospina-Duque, J., Duque, C., Carvajal-Carmona, L., Ortiz-Barrientos, D., Soto, I., Pineda, N., Cuartas, M., Calle, J., Lopez, C., Ochoa, L., et al., 2000. An association study of bipolar mood disorder (type I) with the 5-HTTLPR serotonin transporter polymorphism in a human population isolate from Colombia. Neurosci. Lett 292, 199–202.

Patel, N. C., Cecil, K. M., Strakowski, S. M., Adler, C. M., and DelBello, M. P., 2008. Neurochemical alterations in adolescent bipolar depression: a proton magnetic resonance spectroscopy pilot study of the prefrontal cortex. J Child Adolesc Psychopharmacol 18, 623–627.

Pauls, D. L., Morton, L. A., and Egeland, J. A., 1992. Risks of affective illness among first-degree relatives of bipolar I old-order Amish probands. Arch. Gen. Psychiatry 49, 703–708.

Penttilä, J., Cachia, A., Martinot, J.-L., Ringuenet, D., Wessa, M., Houenou, J., Galinowski, A., Bellivier, F., Gallarda, T., Duchesnay, E., et al., 2009. Cortical folding difference between patients with early-onset and patients with intermediate-onset bipolar disorder. Bipolar Disord 11, 361–370.

Perlis, R. H., Miyahara, S., Marangell, L. B., Wisniewski, S. R., Ostacher, M., DelBello, M. P., Bowden, C. L., Sachs, G. S., and Nierenberg, A. A., 2004. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol. Psychiatry 55, 875–881.

Pillai, J. J., Friedman, L., Stuve, T. A., Trinidad, S., Jesberger, J. A., Lewin, J. S., Findling, R. L., Swales, T. P., and Schulz, S. C., 2002. Increased presence of white matter hyperintensities in adolescent patients with bipolar disorder. Psychiatry Res 114, 51–56.

Post, R. M., Leverich, G. S., Kupka, R. W., Keck, P. E., McElroy, S. L., Altshuler, L. L., Frye, M. A., Luckenbaugh, D. A., Rowe, M., Grunze, H., et al., 2010. Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. J

Clin Psychiatry 71, 864–872.

Post, R. M., Leverich, G. S., Xing, G., and Weiss, R. B., 2001. Developmental vulnerabilities to the onset and course of bipolar disorder. Dev. Psychopathol 13, 581–598.

Priebe, L., Degenhardt, F. A., Herms, S., Haenisch, B., Mattheisen, M., Nieratschker, V., Weingarten, M., Witt, S., Breuer, R., Paul, T., et al., 2011. Genome-wide survey implicates the influence of copy number variants (CNVs) in the development of early-onset bipolar disorder. Mol Psychiatry. Available at: http://dx.doi.org.gate2.inist.fr/10.1038/mp.2011.8 [Accessed March 8, 2011].

Rohayem, J., Baylé, J.-F., and Richa, S., 2008. [Predictors of prophylactic response to lithium]. Encephale 34, 394–399.

Rosa, A. R., Franco, C., Martínez-Aran, A., Sánchez-Moreno, J., Reinares, M., Salamero, M., Arango, C., Ayuso-Mateos, J. L., Kapczinski, F., and Vieta, E., 2008. Functional impairment in patients with remitted bipolar disorder. Psychother Psychosom 77, 390–392.

Schulze, T. G., Hedeker, D., Zandi, P., Rietschel, M., and McMahon, F. J., 2006. What is familial about familial bipolar disorder? Resemblance among relatives across a broad spectrum of phenotypic characteristics. Arch. Gen. Psychiatry 63, 1368–1376.

Schürhoff, F., Bellivier, F., Jouvent, R., Mouren-Siméoni, M. C., Bouvard, M., Allilaire, J. F., and Leboyer, M., 2000. Early and late onset bipolar disorders: two different forms of manic-depressive illness? J Affect Disord 58, 215–221.

Scott, J., 2011. Clinical parameters of circadian rhythms in affective disorders. Eur Neuropsychopharmacol 21 Suppl 4, S671–675.

Scott, J., and Leboyer, M., 2011. [Conséquences du retard diagnostique dans la dépression bipolaire]. Encephale 37 Suppl 3, S173–175.

Severino, G., Manchia, M., Contu, P., Squassina, A., Lampus, S., Ardau, R., Chillotti, C., and Del Zompo, M., 2009. Association study in a Sardinian sample between bipolar disorder and the nuclear receptor REV-ERBα gene, a critical component of the circadian clock system. Bipolar Disorders 11, 215–220.

Smit, D. J. A., Posthuma, D., Boomsma, D. I., and De Geus, E. J. C., 2007. The relation between frontal EEG asymmetry and the risk for anxiety and depression. Biol Psychol 74, 26–33.

Sole, B., Bonnin, C. M., Torrent, C., Martinez-Aran, A., Popovic, D., Tabarés-Seisdedos, R., and Vieta, E., 2011. Neurocognitive Impairment Across the Bipolar Spectrum. CNS Neurosci Ther. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22128808 [Accessed January 14, 2012].

Squassina, A., Manchia, M., Costa, M., Chillotti, C., Ardau, R., Del Zompo, M., and Severino, G., 2011. Age at onset in bipolar disorder: Investigation of the role of TaqIA

polymorphism of DRD2 gene in a Sardinian sample. European Psychiatry 26, 141–143.

Staton, D., 2008. The impairment of pediatric bipolar sleep: hypotheses regarding a core defect and phenotype-specific sleep disturbances. J Affect Disord 108, 199–206.

Tang, J., Xiao, L., Shu, C., Wang, G., Liu, Z., Wang, X., Wang, H., and Bai, X., 2008. Association of the brain-derived neurotrophic factor gene and bipolar disorder with early age of onset in mainland China. Neurosci. Lett 433, 98–102.

Taylor, M. A., and Abrams, R., 1981. Early- and late-onset bipolar illness. Arch. Gen. Psychiatry 38, 58–61.

Tozzi, F., Manchia, M., Galwey, N. W., Severino, G., Del Zompo, M., Day, R., Matthews, K., Strauss, J., Kennedy, J. L., McGuffin, P., et al., 2011. Admixture analysis of age at onset in bipolar disorder. Psychiatry Res 185, 27–32.

Yatham, L. N., Kennedy, S. H., O'Donovan, C., Parikh, S., MacQueen, G., McIntyre, R., Sharma, V., Silverstone, P., Alda, M., Baruch, P., et al., 2005. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. Bipolar Disord 7 Suppl 3, 5–69.

Yatham, L. N., Kennedy, S. H., Schaffer, A., Parikh, S. V., Beaulieu, S., O'Donovan, C., MacQueen, G., McIntyre, R. S., Sharma, V., Ravindran, A., et al., 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disorders 11, 225–255.