Review

Clinical risk factors for bipolar disorders: A systematic review of prospective studies

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A B S T R A C T

Background: Early phases and suspected precursor states of bipolar disorder are not well characterized. We evaluate the prevalence, duration, clinical features and predictive value of non-affective psychopathology as clinical risk factors for bipolar disorder in prospective studies.

Methods: We screened PubMed, CINAHL, PsycINFO, Embase, SCOPUS, and ISI-Web of Science databases from inception up to January 31, 2014, following PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and searched: bipolar disorder AND [antecedent OR predict OR prodrome OR prospect OR risk] AND [diagnosis OR development]. We included only English language reports on prospective, longitudinal studies with two structured clinical assessments (intake and follow-up); no DSM intake diagnosis of bipolar-I or -II; diagnostic outcome was bipolar-I or -II. Details of study design, risk factors, and predictive value were tabulated.

Results: We found 16 published reports meeting selection criteria, with varying study design. Despite heterogeneity in methods, findings across studies were consistent. Clinical risk factors of bipolar disorder were early-onset panic attacks and disorder, separation anxiety and generalized anxiety disorders, conduct symptoms and disorder, ADHD, impulsivity and criminal behavior.

Limitations: Since risk factors identified in some prospective studies are predictive of other conditions besides bipolar disorder, these preliminary findings require replication, and their sensitivity, specificity and predictive value need to be assessed.

Conclusions: Clinical risk factors for bipolar disorder typically arise years prior to syndromal onset, include anxiety and behavioral disorders with unclear sensitivity and specificity. Prospectively identified clinical risk factors for bipolar disorder are consistent with retrospective and family-risk studies. Combining clinical risk factors with precursors and family-risk may improve early identification and timely and appropriate treatment of bipolar disorder.
1. Introduction

Bipolar disorder has an estimated lifetime prevalence of 2.1% (both types I and II) (Merikangas et al., 2011) among US adults, and 1.8% in children and adolescents, both in the US and internationally (Van Meter et al., 2011). It is associated with very high costs (Dilsaver, 2011), high rates of morbidity and mortality, especially among cases with early onset, along with significant disruption of cognitive, behavioral, educational, vocational and interpersonal functioning (Murray and Lopez, 1996; Leverich et al., 2007; Post et al., 2010).

As evidence grows that illness-duration, especially duration of untreated illness, might worsen outcome (Leverich et al., 2007; Post et al., 2010), increased attention has been directed towards early recognition of bipolar disorder as a public health priority (Merikangas et al., 2011; Leverich et al., 2007; Post et al., 2010; Faedda et al., 1995). Also, in retrospective studies, younger age-at-onset is correlated with greater delay of diagnosis and treatment onset, underscoring the importance of timely diagnosis of bipolar disorder in children and adolescents (Leverich et al., 2007).

One of the most important goals of early diagnosis and treatment is preventing the development of comorbid conditions and disability. Untreated bipolar disorder in juveniles increases the risk of addictive, anxiety and other psychiatric disorders, further reducing functioning and quality of life (Duffy, 2010). To address the need for better prediction and earlier recognition of this potentially debilitating chronic illness, in 2011 the International Society for Bipolar Disorder convened a “Task-force on Prodromes of Bipolar Disorder” to review scientific evidence, summarize findings on early psychopathology preceding syndromal bipolar disorder, and make research recommendations. Within that process we have reviewed the research literature on prodromal features of bipolar disorder, both affective features (Faedda et al., 2013) and non-affective symptoms. In the present review, we focused on prospective studies of non-affective psychopathology or clinical risk factors (Fig. 1) that may help characterize the pre-syndromal or prodromal phase of bipolar disorder.

Research questions were: 1) is there evidence of a prodromal phase of bipolar disorder in prospective studies? 2) Are there specific premorbid clinical risk factors (non-affective signs and symptoms) that predict bipolar disorder? 3) What are the nature, timing, and duration of these factors? 4) How sensitive and specific are these clinical risk factors in predicting later diagnosable bipolar disorder? 5) Do prodromal phases differ by subtype (bipolar-I vs. bipolar-II)?

The prodromal features of bipolar disorder are also of great clinical interest also due to the resemblance of manic symptoms to the externalizing symptoms seen in childhood disruptive behavior disorders, and of anxiety and depressive symptoms of internalizing disorders. An alternative approach has used general measures of psychopathology (e.g. Child Behavior Checklist [CBCL]), family history of mood disorders or other diagnoses to identify populations at risk, again with limited predictive value (Duffy, 2010; Papachristou et al., 2013).

The relationship between bipolar disorder and early anxiety, disruptive behavior or substance use symptoms or disorders is difficult to clarify, and is often attributed to comorbidity. However, in the early course of bipolar disorder, it might be impossible to determine when these are truly independent co-occurring conditions or clinical manifestations of pre-syndromal bipolar disorder.

Given the limitations of alternative methods, only prospective observation of populations at risk can adequately assess the predictive value of proposed risk factors.

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Research questions were: 1) is there evidence of a prodromal phase of bipolar disorder in prospective studies? 2) Are there specific premorbid clinical risk factors (non-affective signs and symptoms) that predict bipolar disorder? 3) What are the nature, timing, and duration of these factors? 4) How sensitive and specific are these clinical risk factors in predicting later diagnosable bipolar disorder? 5) Do prodromal phases differ by subtype (bipolar-I vs. bipolar-II)?
2. Methods

2.1. Data sources

We conducted a systematic literature review of studies investigating non-affective symptoms and clinical features prior to a diagnosis of bipolar disorder according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines. The review was eligible for registration with PROSPERO (http://www.crd.york.ac.uk/NIHR_PROSPERO/), an international database of prospectively registered systematic reviews in health and social care. We searched PubMed, CINAHL, PsycINFO, Embase, SCOPUS, and ISI-Web of Science databases from inception until January 31, 2014. Search-terms were combinations of these subject headings: bipolar disorder AND [antecedent OR predict OR prodrom OR risk] AND [diagnosis OR development].

2.2. Study selection and data extraction

Inclusion criteria were: 1) prospective, longitudinal studies with at least two structured clinical assessments (intake and follow-up); 2) diagnostic outcome at follow-up as bipolar-I or -II disorder based on DSM-III or -IV criteria. Exclusion criteria were: 1) subjects with a pre-intake lifetime DSM diagnosis of mood or psychotic disorder; 2) studies of exposure to trauma (such as prenatal injuries, earlier trauma or abuse, substance abuse, exposure to potential toxins); 3) studies of genetic abnormalities; 4) studies of neuropsychological or neuroimaging risk factors; 5) family-risk studies (offspring of parents/siblings of subjects with bipolar disorder); 6) studies of temperaments or personality disorders; 7) pharmacological trials; and 8) case reports or reviews.

Three clinical investigators (GLF, GS, CM) screened search results, applied inclusion and exclusion criteria and resolved discrepancies to unanimous consensus. Data extraction was completed independently by the three investigators and entered in an Excel file including: report reference, reporting year, number of subjects, type of study, initial diagnosis (if any), assessment tool used, duration of follow-up, rate of diagnostic change, risk factors examined, statistics (usually based on Odds Ratios [OR], Hazard Ratios [HR], or Likelihood Ratios [LR]), annotations. Differences between findings by individual investigators were resolved by consensus, followed by summarization and re-verification by all three reviewers.

3. Results

We located 16 original reports meeting inclusion criteria. A flow-chart of reports considered, excluded, and included for analysis is summarized in Fig. 2. Several clinical risk factors were associated with an elevated risk of bipolar disorder. These included anxiety symptoms and disorders, conduct symptoms and disorders, ADHD, oppositional-defiant disorder, impulsivity, and aggressive behaviors. A summary of relevant findings is presented in Table 1.

3.1. Anxiety symptoms and disorders

In a community study, any lifetime anxiety disorder in adolescents was a significant risk factor for bipolar disorder (Johnson et al., 2000).

3.2. Generalized anxiety disorder

In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), among subjects with elation and/or irritability at intake, generalized anxiety disorder predicted later hypomania (Homish et al., 2013).

3.3. Separation anxiety

A specific association of separation anxiety with bipolar-I and II, but not with major depression was reported (Brückl et al., 2007). Sub-threshold separation anxiety increased the risk of bipolar-II but not of bipolar-I or major depression. In prospectively
observed cases, sub-threshold or syndromal separation anxiety predicted the first onset of bipolar-II disorder more strongly than other disorders, including panic attack, alcohol dependence and pain disorder (Brückl et al., 2007).

3.4. Panic attacks

In the NESARC, subjects without panic disorder at intake who developed panic attacks were at increased risk for bipolar disorder (Kinley et al., 2011).

3.5. Post-traumatic stress disorder

Post-traumatic stress disorder at baseline predicted bipolar-I in the NESARC study (Grant et al., 2009; Chou et al., 2011).

3.6. Disruptive behavior disorders

Adolescents with a disruptive behavior disorder were at increased risk of bipolar disorder within 8–9-years in two community studies (Johnson et al., 2000; Tijssen et al., 2010).

3.7. Conduct symptoms and disorder

Sub-syndromal conduct disorder predicted bipolar disorder even after adjusting for comorbidity, in a 15-year follow-up of youths (Shankman et al., 2009), a finding replicated in youth in the NESARC study (Morcillo et al., 2012). Furthermore conduct/oppositional defiant disorder in childhood preceded adult bipolar disorder in the Dunedin birth-cohort, with a population attributable fraction of 22% (Kim-Cohen et al., 2003).

3.8. Impulsivity and criminal behavior

Prospective observations suggest an association between early impulsivity and later bipolar disorder, even after controlling for family history of bipolar spectrum disorders (Alloy et al., 2012).

In addition, a significant association was reported between criminal behaviors and sub-threshold and syndromal bipolar disorder in the Early Developmental Stages of Psychopathology study (EDSP) (Zimmermann et al., 2009).
3.9. Attention Deficit Hyperactivity Disorder

Baseline ADHD predicted bipolar-I disorder in the NESARC study (Grant et al., 2009), while in an outpatient cohort study, children diagnosed with ADHD at baseline had significantly higher rates of bipolar disorder compared to controls: 6% at 1-year, and 12% at 4-years of follow-up (Biederman et al., 1996a). A baseline comorbidity of ADHD with conduct disorder and/or oppositional-defiant disorder increased the risk of later bipolar disorder compared to ADHD alone and normally developing controls (Biederman et al., 1996b, 2008). Prospectively observed cases of ADHD had increased rates of comorbidity (conduct, oppositional-defiant, anxiety and major depressive disorders) before developing bipolar disorder, with more ADHD symptoms, higher CBCL ratings, higher rates of family history of mood disorders, and increased rates of psychosis and substance abuse (not observed in those with bipolar disorder at intake) (Biederman et al., 1996a, 1996b, 2008).

Table 1
Clinical risk factors for bipolar disorder.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study year</th>
<th>Subjects (N)</th>
<th>Age range (mean), y</th>
<th>Dx criteria/assessment tool</th>
<th>Design</th>
<th>Follow up, range (mean), y</th>
<th>OR/AOR/fn;a</th>
<th>HR/LR/b; p-value/</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any anxiety</td>
<td>Johnson et al., 2000</td>
<td>717</td>
<td>14–22</td>
<td>DSM-III-R/DISC</td>
<td>Community</td>
<td>9</td>
<td>4.69</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Generalized anxiety</td>
<td>Honish et al., 2013</td>
<td>1090</td>
<td>&gt; 18</td>
<td>DSM-IV/ AUDADIS-IV</td>
<td>Community</td>
<td>(3)</td>
<td>3</td>
<td>2.1</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>PTSD &gt; BD-I</td>
<td>Grant et al., 2009</td>
<td>34,653</td>
<td>&gt; 18</td>
<td>DSM-IV/ AUDADIS-IV</td>
<td>Community</td>
<td>(3)</td>
<td>3</td>
<td>2.4</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>PTSD &gt; BD-II</td>
<td>Chou et al., 2011</td>
<td>8012</td>
<td>&gt; 60</td>
<td>DSM-IV/ AUDADIS-IV</td>
<td>Community</td>
<td>(3)</td>
<td>3.35</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Separation anxiety &gt; BD-I</td>
<td>Bruckl et al., 2007</td>
<td>1090</td>
<td>14–24</td>
<td>DSM-IV/M-CIDI</td>
<td>Community</td>
<td>(EDSP)</td>
<td>4</td>
<td>6.29</td>
<td>Retrospectively reported</td>
</tr>
<tr>
<td>Separation anxiety &gt; BD-II</td>
<td>Bruckl et al., 2007</td>
<td>1090</td>
<td>14–25</td>
<td>DSM-IV/M-CIDI</td>
<td>Community</td>
<td>(EDSP)</td>
<td>4</td>
<td>8.59</td>
<td>Retrospectively reported</td>
</tr>
<tr>
<td>Subsyndromal separation anxiety &gt; BD-II</td>
<td>Bruckl et al., 2007</td>
<td>1090</td>
<td>14–26</td>
<td>DSM-IV/M-CIDI</td>
<td>Community</td>
<td>(EDSP)</td>
<td>4</td>
<td>8.19</td>
<td>Retrospectively reported</td>
</tr>
<tr>
<td>Subsyndromal &amp; syndromal separation anxiety &gt; BD-II</td>
<td>Kinley et al., 2011</td>
<td>34,653</td>
<td>&gt; 18</td>
<td>DSM-IV/ AUDADIS-IV</td>
<td>Community</td>
<td>(NESARC)</td>
<td>(3)</td>
<td>2.39</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Panic attacks/disorder</td>
<td>Johnson et al., 2000</td>
<td>717</td>
<td>&gt; 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disruptive behavioral disorders &gt; mania</td>
<td>Tijsen et al., 2010</td>
<td>1902 risk set</td>
<td>14–24</td>
<td>DSM-IV/M-CIDI</td>
<td>Community</td>
<td>(EDSP)</td>
<td>7.3–10.6 (8.3)</td>
<td>5.29</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Disruptive behavioral disorders &gt; hypomania</td>
<td>Tijsen et al., 2010</td>
<td>1902 risk set</td>
<td>14–24</td>
<td>DSM-IV/M-CIDI</td>
<td>Community</td>
<td>(EDSP)</td>
<td>7.3–10.6 (8.3)</td>
<td>7.82</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>ADHD &gt; mania</td>
<td>Biederman et al., 1996a</td>
<td>260</td>
<td>&gt; 18</td>
<td>DSM-III-R/K-SADS-E</td>
<td>Outpatients cohort</td>
<td>(EDSP)</td>
<td>(4)</td>
<td>NA</td>
<td>12% conversion rate, p &lt; 0.01</td>
</tr>
<tr>
<td>ADHD vs. no ADHD</td>
<td>Biederman et al., 2008</td>
<td>260</td>
<td>6–17</td>
<td>DSM-III-R/K-SADS-E</td>
<td>Outpatients cohort</td>
<td>(EDSP)</td>
<td>(10)</td>
<td>NA</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>ADHD + ODD vs. no ADHD</td>
<td>Biederman et al., 2008</td>
<td>260</td>
<td>6–17</td>
<td>DSM-III-R/K-SADS-E</td>
<td>Outpatients cohort</td>
<td>(EDSP)</td>
<td>(10)</td>
<td>NA</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>ADHD &gt; mania</td>
<td>Grant et al., 2009</td>
<td>34,653</td>
<td>&gt; 18</td>
<td>DSM-IV/ AUDADIS-IV</td>
<td>Community</td>
<td>(NESARC)</td>
<td>(3)</td>
<td>2.6</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Conduct/oppositional defiant disorder &gt; mania</td>
<td>Kim-Cohen et al., 2003</td>
<td>976</td>
<td>NA</td>
<td>DSM-III-R/DISC</td>
<td>Birth cohort (Dunedin study)</td>
<td>(OADP)</td>
<td>23</td>
<td>2.59</td>
<td>a; AFP = 22%</td>
</tr>
<tr>
<td>Conduct disorder and ADHD vs. ADHD w/o CD</td>
<td>Biederman et al., 1996b</td>
<td>260</td>
<td>6–17</td>
<td>DSM-III-R/K-SADS-E</td>
<td>Outpatients cohort</td>
<td>(OADP)</td>
<td>(4)</td>
<td>NA</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Conduct disorder and ADHD vs. ADHD + ODD w/o CD</td>
<td>Biederman et al., 2008</td>
<td>260</td>
<td>6–17</td>
<td>DSM-III-R/K-SADS-E</td>
<td>Outpatients cohort</td>
<td>(OADP)</td>
<td>(10)</td>
<td>NA</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Conduct disorder-subsyndromal</td>
<td>Shankman et al., 2009</td>
<td>1505</td>
<td>14–20</td>
<td>DSM-IV/K-SADS-E</td>
<td>Community</td>
<td>(OADP)</td>
<td>15</td>
<td>3.9</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>Morcillo et al., 2012</td>
<td>34,653</td>
<td>&gt; 18</td>
<td>DSM-IV/ AUDADIS-IV</td>
<td>Community</td>
<td>(NESARC)</td>
<td>(3)</td>
<td>2.04 M, 1.72 F</td>
<td></td>
</tr>
<tr>
<td>Criminal behavior</td>
<td>Zimmermann et al., 2009</td>
<td>2210 risk set</td>
<td>14–24</td>
<td>DSM-IV/ AUDADIS-IV</td>
<td>Community</td>
<td>(NESARC)</td>
<td>(3)</td>
<td>1.68</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Impulsivity-hypomaniac sx-FamHx (BD-I)</td>
<td>Alloy et al., 2012</td>
<td>57 cyclothymia or BD-NOS</td>
<td>18–24</td>
<td>DSM-IV/ exp-SADS-L</td>
<td>Community</td>
<td>(LIBS)</td>
<td>(4,5)</td>
<td>1.21</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Impulsivity-hypomaniac sx (BD-I)</td>
<td>Alloy et al., 2012</td>
<td>57 cyclothymia or BD-NOS</td>
<td>18–24</td>
<td>DSM-IV/ exp-SADS-L</td>
<td>Community</td>
<td>(LIBS)</td>
<td>(4,5)</td>
<td>1.21</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>Chamorro et al., 2012</td>
<td>34,653</td>
<td>&gt; 18</td>
<td>DSM-IV/ AUDADIS-IV</td>
<td>Community</td>
<td>(NESARC)</td>
<td>(3)</td>
<td>3.19</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>


a Adjusted Odds Ratios.
b Likelihood Ratios.
c Adjusted Hazard Ratios.
4. Discussion

This review of prospective studies on clinical risk factors for bipolar disorder yields several notable findings (Table 1). We found evidence of a range of psychopathological symptoms and behavioral changes that are proposed as a prodromal phase of bipolar disorder. This conclusion is consistent with findings of retrospective studies. We review the findings and put them in the context of available data from retrospective and family-risk studies.

The association of anxiety disorder with prospectively observed bipolar disorder was confirmed by several studies (Johnson et al., 2000; Homish et al., 2013; Brückl et al., 2007; Kinley et al., 2011; Grant et al., 2009; Chou et al., 2011). Such a predictive association was especially strong with separation anxiety (Brückl et al., 2007) and early-onset fearful panic attacks (Kinley et al., 2011), a finding confirmed among adults with bipolar-I in the NESARC study (Goldstein and Levitt, 2007). Early-onset panic anxiety with fearful response (EF, defined as onset of panic attack ≤ 20 year with cognitive fear) was associated with high risk of bipolar disorder in the National Comorbidity Survey (NCS) (Goodwin and Hamilton, 2002a). Using multiple logistic regression analyses of Epidemiological Catchment Area (ECA) data, Goodwin and Hamilton (2002b) showed that EF panic was independently associated with a diagnosis of bipolar disorder and schizophrenia. Adolescents with an anxiety disorder had elevated risk for sub-threshold or syndromal bipolar disorder during early adulthood (Johnson et al., 2000); similarly, in young adults, especially males, separation anxiety disorder increased the odds of bipolar disorder (Lewinsohn et al., 1997). Additionally, any lifetime anxiety disorder was a significant risk factor for bipolar disorder in adults with euphoric-grandiose bipolar-I in the NCS (Kessler et al., 1997) and in adults with bipolar-I in the NESARC (Goldstein and Levitt, 2007). Moreover, the association was independent of age of onset in the Canadian Community Health Survey (CCHS), (Schaffer et al., 2010) and in the NESARC study (Moreno et al., 2012). This is not surprising, given the high rates of comorbidity with anxiety disorders found in retrospective studies of adults with bipolar disorder (Merikangas et al., 2011; Leverich et al., 2007; Angst et al., 2010). The association of anxiety disorder with later bipolar disorder was also confirmed by prospective studies of offspring of adults with bipolar disorder: anxiety disorders are among the earliest psychopathology (Duffy, 2010; Egeland et al., 2012; Mesman et al., 2013). Anxiety disorders might be markers of general psychopathology, given their earlier age of onset in childhood as compared to disruptive behavior, mood disorders and substance abuse disorders (Merikangas et al., 2010).

We found some evidence for increased risk of bipolar disorder in youth with conduct symptoms and disorders, aggressive behaviors, including runaway behavior, truancy, frequent physical fights, bullying, aggression or violence, as well as crime and incarceration (Shankman et al., 2009; Johnson et al., 2000; Tijsen et al., 2010; Morcillo et al., 2012; Kim-Cohen et al., 2003; Zimmerman et al., 2009; Pulay et al., 2008). Bullying and firesetting weakly increased the risk of bipolar disorder (compared to the risk for conduct or antisocial personality disorders) in the NESARC study (Vaughn et al., 2010; Blanco et al., 2011).

This association is supported by the findings in the NCS study that conduct disorder significantly predicted bipolar-I (with euphoria or grandiosity) (Kessler et al., 1997) and with retrospective reports of frequent aggression, explosive temper, hyperactivity and behavioral difficulties in children later diagnosed with bipolar disorder (Faedda et al., 1995, 2004; Papachristou et al., 2013; Fergus et al., 2003). For instance, before age 3, an irritability/discontrol factor (characterized by temper tantrums, poor frustration tolerance, impulsivity, increased aggression, decreased attention span, hyperactivity, and irritability) differentiated children with bipolar disorder from those with ADHD and normally developing controls (Fergus et al., 2003). Interestingly, the association between disruptive behavior disorders and later onset of bipolar disorder was not found in prospective studies of children at family risk for bipolar disorder, in which subjects had low rates of ADHD and disruptive behavioral disorders (Duffy, 2010; Egeland et al., 2012; Mesman et al., 2013).

Attention and behavioral difficulties in childhood have consistently been found in prospective studies (Grant et al., 2009; Tijsen et al., 2010; Kim-Cohen et al., 2003; Biederman et al., 1996a, 1996b, 2008; Gau et al., 2010). Childhood ADHD was found to predict adolescent mood disorders, bipolar disorder, disruptive behavior disorders (both conduct and oppositional defiant), sleep disorders and specific phobias (Gau et al., 2010). Others confirmed this association in retrospective studies with some evidence of a significant negative interaction (Bernardi et al., 2012). In fact, early onset of bipolar disorder is reported to be more frequent in children with comorbid ADHD, and might indicate a particular phenotype of bipolar disorder with an early onset, high comorbidity, irritability and impairment and possibly poorer response to treatment (Bernardi et al., 2012).

Several studies have documented a positive correlation between impulsivity and aggression ratings in bipolar disorder, and mania is over-represented among assaultive and first-psychosis inpatients (Dean et al., 2007; Najt et al., 2007). Also, retrospectively assessed violent behavior before and after age 15 was associated with bipolar disorder in the NESARC study (Pulay et al., 2008). Indeed, bipolar disorder significantly increased the likelihood of being incarcerated, while ADHD and conduct disorder decreased it (Stoddard Dare et al., 2011). The high rates of bipolar disorder among incarcerated youth (Mallett et al., 2009) and the association of bipolar disorder with committing a personal crime (Zimmermann et al., 2009; Stoddard Dare et al., 2011) are intriguing and might suggest that early psychopathology involving impulsivity and aggression in patients with bipolar disorder increases the risk of incarceration.

The association of anxiety disorders (separation anxiety, social phobia and early-onset fearful panic attacks) and disruptive behavior disorders (ADHD, conduct disorder) with bipolar disorder suggests that prodromal features extend well beyond homotypic development from affective precursors of bipolar disorder (Faedda et al., 2013; Shankman et al., 2009), with evidence of a heterotypic development from sub-syndromal and syndromal anxiety and disruptive behavior disorders to bipolar disorder.

There was some evidence of association by bipolar subtype as subsyndromal separation anxiety predicted only bipolar-II (Brückl et al., 2007), while PTSD predicted only bipolar-I (Grant et al., 2009; Chou et al., 2011; Kessler et al., 1997). Disruptive behavior disorders predict bipolar-I (Johnson et al., 2000) and both, bipolar-I and -II (Tijsen et al., 2010). Conduct symptoms were associated with mania (Kim-Cohen et al., 2003; Kessler et al., 1997) but also hypomania (Pulay et al., 2008), with a specific association between retrospectively assessed conduct problems and bipolar-II (Endrass et al., 2007).

ADHD was associated with later development of mania (Grant et al., 2009; Biederman et al., 2008) and impulsivity was specifically associated with later bipolar-I in outpatient with BD-NOS (Alloy et al., 2012).

Our results point to different trajectories of psychopathology preceding bipolar disorder. Besides a homotypic evolution from attenuated affective symptoms (Faedda et al., 2013), at least two heterotypic trajectories are compatible with these results. In the data reviewed, anxiety disorders often preceded hypomania or mania, but the specificity of these findings is unclear, and it remains uncertain whether anxiety is a co-morbid condition or a part of the possible manifestations of bipolar disorder.

Another trajectory was characterized by dysphoric and mixed features, high impulsivity and aggression, presence of negativistic
and oppositional tendencies result in diagnoses of disruptive and behavioral disorders, involvement with the legal system, and incarceration. The relative frequency of conduct problems, criminal behaviors and impulsivity in some prospective studies (Tijssen et al., 2010; Alloy et al., 2012; Zimmermann et al., 2009) as well as its association with incarceration warrants additional research to help clarify its frequency and relationship to bipolar disorder.

4.1. Limitations

Several considerations should be taken into account in the interpretation of the results. The association between risk factors and bipolar disorder does not indicate a causal relationship and, in the natural history of bipolar disorder, the onset of symptoms might occur after a latent (asymptomatic) period. Therefore, the appearance of observable psychopathology might be a relatively late manifestation of etiological factors already operating in the illness’ development. Furthermore, although prospective observation was used, the presence of symptoms or diagnoses before the first assessment (lifetime diagnoses) was determined retrospectively, possibly introducing recall bias. Few studies provided risk ratios, but many reported odds ratios. In epidemiological case-control studies, when the prevalence of the disease is low (<10%) the rare disease assumption postulates that the odds ratio approaches the relative risk, providing a good estimate of its size. Despite statistical associations with later bipolar disorder diagnoses, there appeared to be evidence of limited specificity of some non-affective clinical precursors considered here, for predicting later bipolar versus other disorders. Since risk factors identified in some prospective studies are predictive of disorders other than bipolar disorder, their associations require further testing, and their sensitivity, specificity and predictive value need to be assessed. In most studies, the duration of follow-up was relatively short, and many subjects were still young adults at the end of the follow-up, possibly leading to lower estimates of adult diagnoses. In addition, current understanding of the effect of risk factors identified as preceding bipolar disorder on normal development remains very limited, as does the relationship of specific risk factors to clinical details of the final illness. Also, the timing, duration, and sequencing of specific types of prodromal manifestations before the diagnosis of bipolar disorder remain uncertain. We could not assess the significance of possible interactions or cumulative effects of particular types of precursors and clinical risk factors with each other, or with family history, or other risk factors or environmental exposures. In general, it is not clear whether specific factors are early manifestations of what will later be diagnosed as bipolar disorder or, instead, risk factors or predictors of this and perhaps other later disorders.

5. Conclusions

There is preliminary evidence from the literature reviewed of a heterotypic development of bipolar disorder. Bipolar disorder is often preceded by clinical risk factors such as anxiety and disruptive behavior symptoms and disorders. Further evaluation of the predictive value of such clinical risk factors for bipolar disorder can help identify populations at increased risk, guide timely interventions, and perhaps reduce the morbidity, mortality and improve its treatment response and outcome.

Conflict of interest

Disclosures: None of the authors or their immediate family members has a potential conflict of interest in the work presented here. Drs. Faedda, Serra, Marangoni, Salvatore, Sani, Vázquez, Tondo, Girardi, Baldessarini, and Koukopoulos report no financial relationships with commercial interests.

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