Determinants of long-term course in Bipolar disorder

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To
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ABSTRACT

Introduction: Bipolar disorder (BP) is a common and severe psychiatric illness with a high variability. An early treatment is often crucial for a good prognosis and it is difficult for clinicians to define high risk patients in order to predict a more severe course. Our aim was to investigate factors predicting the long-term course of BP.

Methods: We have retrospectively investigated the course of illness in parallel with life-events and pharmacological treatment in 100 BP patients, using a life-charting program. Predictors and their impact on the outcome of lithium treatment were analyzed (Paper I). We then used the Swedish in-patient registry to study the annual incidence rate of BP patients hospitalized for the first time during 1997-2005 (Paper II). We also monitored the readmission rates during five years of patients who had their first or second admission for bipolar episodes during year 2000 (Paper II). Further, two groups of BP patients were recruited for molecular genetic studies. Manic symptoms were assessed and phenotype variations such as mixed episodes (ME), rapid cycling (RC), and the age at onset were defined. Using association analysis, patients with specific symptoms/phenotypes were compared to the other bipolar patients for genetic markers in one small sample. Positive associations identified were then searched for in a larger second sample (Papers III and IV).

Results: The number of episodes decreased after the introduction of lithium. An early onset was associated with a longer time until treatment (18.1 vs. 10.7 years). The most important predictors for a poor outcome during treatment were RC (OR=10.7), comorbidity (OR=3.8), and ME (OR=2.8) (Paper I). The average length of stay during the first hospitalization was 42 days for ME compared to 30 days for other episodes. Of the 874 participants who had had their first admission for a bipolar episode in 2000, 44% had at least one readmission during the 5-year follow-up. A small group (15%) accounted for 66% of the re-admissions (Paper II). Utilizing molecular genetics, cognitive symptoms in mania were found to be associated with the SNP rs1718119 (p<0.0006; Paper III), and RC with the SNP rs2230912 (p<0.004; paper IV), both SNPs being located in the P2RX7 gene. Combining the SNP rs2230912 in the P2RX7 gene and the previously associated rs10838524 in the CRY2 gene in an epistasis analysis yielded evidence of a strong association with RC (p=0.00005; OR=7.4).

Conclusions: The life-charting methodology can be useful in studying the long-term course of BP. A limitation is that the multitude of data on each studied patient limits the possibility of dealing with large samples. Our findings support the results of previous studies suggesting that RC, ME and comorbidity for other Axis I disorders are predictors for a more severe course of illness. Most of the first admitted BP patients were not readmitted in the subsequent 5-year period. Our genetic findings suggest that different symptoms and phenotypes in BP are associated with specific genes, making the biological pathways behind BP more transparent. The finding that BP patients with a specific combination of variations in the P2RX7 and CRY2 genes run a 7-fold greater risk of developing RC that those patients not having this combination, is a new contribution to the research field, which increases the possibility of identifying patients who risk developing a more severe course of BP.
PAPERS IN THE PRESENT THESIS


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ABBREVIATIONS

ADHD  Attention Deficit and Hyperactivity Disorder
BP    Bipolar disorder
BPNF  Brain-Derived Neurotrophic Factor
COMT  Catechol-O-Methyltransferase
DSM-IV Diagnostic and Statistical Manual for Mental Disorders, revised form
ME    Mixed Episodes
LCM   The Life-Charting Methology
LD    Linkage Disequilibrium
       Logarithm of Odds
OR    Odds Ratio
RC    Rapid Cycling
SNP   Single Nucleotide Polymorphism
INTRODUCTION

Bipolar disorder or Manic Depressive Illness is a common psychiatric illness described in antiquity by Hippocrates (460–370 BC) and Aristotle. Aretaeus of Cappodochia (2nd century AD) seems to have been the first to bring the symptoms of melancholia and depression together. Emil Kraepelin built the first modern diagnostic system for psychiatric disorders and differentiated Manic-Depressive Insanity from Dementia praecox (later to be renamed schizophrenia by Bleuler) in his well-known textbook *Depressive Insanity and Paranoia* (Kraepelin 1921). He also pointed out the necessity of making long-term observations of manic–depressive illness, and made incisive clinical observations greatly influencing what we know today about bipolar disorder. Kraepelin was succeeded by Karl Leonard, Jules Angst and Carlo Perris, all of whom made seminal contributions to our understanding of the long-term course of bipolar disorder. Today the research into this illness is vast, but investigations about long-term course and predictors for the outcome of bipolar disorder are quite scarce.

The severity and duration of episodes, signs and outcome of the illness vary considerably. The more severe forms of bipolar disorder may be difficult to treat and the suicide rate is high. It is still difficult for clinicians to identify high-risk patients at an early stage and to be able to predict the risk for future worsening. Furthermore, there is a need to individualize the treatment according to the course and symptoms of the illness. The aim of this project was to investigate the importance of different predictors for the long-term course of bipolar disorder.
Bipolar Disorder

Bipolar disorder is one of the most common and severe psychiatric disorders. It is a prevalence ranging from 0.2% to 2.0% for the more severe illness with depressions and full-blown manias, i.e. Bipolar disorder type 1, and 1% to 3% for bipolar illnesses with depressions and milder forms of mania i.e. Bipolar disorder type 2 (Goodwin and Jamison 2007). The mean age at onset of illness is 21 years, similar in men and women, and more than 80% of the patients having a first episode will suffer a recurrence (Winokur et al. 1994). In most cases, the course of the disease is progressive and the suicide frequency is high, ranging from 11 to 19% (Tondo et al. 1999; Ösby et al. 2001; Tondo et al. 2003). The early symptoms of bipolar disorder can be discrete and the diagnosis is therefore difficult to make. According to earlier studies, 40-90% of the cases are misdiagnosed or are not diagnosed at all (Regier et al. 1988; Das et al. 2005). On average, there is a period of five years between onset and the first consultation, and the delay from onset to the introduction of mood stabilizers is ten years or more (Bryant-Comstock et al. 2002). This delay may be ominous, since early diagnosis and the instigation of pharmacological treatment may be crucial to avoid suffering from several illness episodes with serious social, psychological and cognitive consequences.

Symptoms of Bipolar disorder

Bipolar disorder, also referred to as manic-depressive illness, is characterized by at least one manic episode or a mixed episode with both depressive and manic symptoms. Most individuals also suffer from recurrent episodes of depressions too (Table 1). The severity and duration of episodes, and the signs and outcome of the illness vary considerably. There is a spectrum of bipolar disorders from the most severe form comprising severe episodes necessitating in-patient treatment to less severe forms often needing no treatment at all, i.e. cyclothymia. Mixed episodes can be seen in both Bipolar disorder type 1 and type 2.
Table 1. DSM-IV criteria for bipolar episodes

<table>
<thead>
<tr>
<th>Depressive episode</th>
<th>Manic episode</th>
<th>Mixed episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Five (or more) of the following symptoms have been present during the same</td>
<td>A. A distinct period of abnormally and persistently elevated,</td>
<td>A. The criteria are met both for a Manic Episode and for a Major Depressive</td>
</tr>
<tr>
<td>2-week period and represent a change from previous functioning; at least one of</td>
<td>expansive, or irritable mood, lasting at least 1 week (or any duration if</td>
<td>Episode nearly every day during at least a 1-week period. (At least 2 manic</td>
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<tr>
<td>the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.</td>
<td>hospitalization is necessary).</td>
<td>symptoms during mania).</td>
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<tr>
<td>1. Depressed mood</td>
<td>B. During the period of mood disturbance, three (or more) of the following</td>
<td>B. The mood disturbance is sufficiently severe to cause marked impairment in</td>
</tr>
<tr>
<td>2. Markedly diminished interest or pleasure</td>
<td>symptoms have persisted (four if the mood is only irritable) and have been</td>
<td>occupational functioning or in usual social activities or relationships with</td>
</tr>
<tr>
<td>3. Appetite or weight changes</td>
<td>present to a significant degree:</td>
<td>others, or to necessitate hospitalization to prevent harm to self or others,</td>
</tr>
<tr>
<td>4. Insomnia/hypersomnia</td>
<td>1. Inflated self-esteem/grandiosity</td>
<td>or there are psychotic features.</td>
</tr>
<tr>
<td>5. Psychomotor agitation/retardation</td>
<td>2. Decreased need for sleep</td>
<td>C. The symptoms are not due to the direct physiological effects of a substance</td>
</tr>
<tr>
<td>6. Fatigue/loss of energy</td>
<td>3. Talkativeness</td>
<td>or a general medical condition.</td>
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<td>7. Feelings of worthlessness/excessive/inappropriate guilt</td>
<td>4. Flight of ideas/subjective experience that thoughts are racing</td>
<td></td>
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<td>8. Diminished ability to think/concentrate</td>
<td>5. Distractability</td>
<td></td>
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<tr>
<td>9. Recurrent thoughts of death/suicidal ideation</td>
<td>6. Increased goal-directed activity/psychomotor agitation</td>
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<td></td>
<td>7. Excessive involvement in pleasurable activities that have a high potential</td>
<td></td>
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<td></td>
<td>for painful consequences</td>
<td></td>
</tr>
<tr>
<td>B. The symptoms do not meet the criteria for a Mixed Episode.</td>
<td>C. The symptoms do not meet the criteria for a Mixed Episode.</td>
<td></td>
</tr>
<tr>
<td>C. The symptoms cause clinically significant distress or impairment in social,</td>
<td>D. The mood disturbance is sufficiently severe to cause marked impairment in</td>
<td></td>
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<tr>
<td>occupational, or other important areas of functioning.</td>
<td>occupational functioning or in usual social activities or relationships with</td>
<td></td>
</tr>
<tr>
<td>D. The symptoms are not due to the direct physiological effects of a substance</td>
<td>others, or to necessitate hospitalization to prevent harm to self or others,</td>
<td></td>
</tr>
<tr>
<td>(e.g., a drug of abuse, a medication) or a general medical condition (e.g.,</td>
<td>or there are psychotic features.</td>
<td></td>
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<tr>
<td>hypothyroidism).</td>
<td></td>
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<tr>
<td>E. The symptoms are not better accounted for by bereavement, i.e., after the</td>
<td></td>
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<td>loss of a loved one, the symptoms persist for longer than two months or are</td>
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<tr>
<td>characterized by marked functional impairment, morbid preoccupation with</td>
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<td>worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.</td>
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Etiology

It is generally accepted that the etiology of bipolar disorder is complex. There are obviously combinations of environmental as well as genetic factors behind the disorder. Several previous studies have presented strong evidence for a genetic predisposition but other important factors are life-events and stress (Frank 1994; Mazure 1995), personality traits (Bagby et al. 1996; Bagby et al. 1997; Hecht et al. 1998; Engström et al. 2003) and family factors (Miklowitz et al. 1988).

Genetics

Twin- and adoption studies since the early 1960’s have shown a familial aggregation of bipolar disorder. Epidemiological research in Sweden has identified that relatives to bipolar patients and adopted children from these parents have an increased risk of both bipolar disorder and schizophrenia (Lichtenstein et al. 2009). Monozygotic twins have a concordance rate of 40-45 % for bipolar disorder to 4.5-5.6 % for dizygotic twins, and the risk of illness for first degree relatives of bipolar patients is nearly 10-fold greater than that of the general population (Tsuang et al. 1985; Pauls et al. 1992; Joyce et al. 2004; Kieseppa et al. 2004). The heritability is estimated to be 79-93%, which establishes bipolar disorder as one of the most heritable among polygenic medical disorders (McGuffin et al. 2003). All these findings support a familial risk, but it has been difficult to identify individual genes in the etiology of bipolar disorder.

The exact genetic constitution of a cell, an organism or an individual, i.e. the genotype, in combination to environmental factors, forms the observable characteristics of an individual, such as properties, behavior or traits, i.e. phenotype. In psychiatric genetics there is a need to define behavioral symptoms into more stable phenotypes with a genetic connection, i.e. endophenotypes (Gottesman and Gould 2003). Five criteria must be fulfilled for a biomarker or a cognitive marker to be called an endophenotype:

- The endophenotype is associated with illness in the population
The endophenotype is heritable.

The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active).

Within families, the endophenotype and illness co-segregate.

The endophenotype found in affected family members is also found in non-affected family members at a higher rate than in the general population.

Other terms with similar meaning but not stressing the genetic connection, are intermediate phenotype, biological marker, subclinical trait, vulnerability marker and cognitive marker.

**Candidate genes**

Several genes such as *S100A10* (p11;1q21) (Svenningsson et al. 2006), *BPNF* (11p13) (Sklar et al. 2002; Nakata et al. 2003; Skibinska et al. 2004), *P2RX7* (12q24) (Barden et al. 2006; Erhardt et al. 2007; Bass et al. 2009; Hejjas et al. 2009), *CAMKK2* (12q24.2) (Anderson et al. 2008), *DAOA* (13q34) (Williams et al. 2006; Prata et al. 2008; Bass et al. 2009), *SLC6A4* (serotonin transporter: 17q11.1-q12) (Sun et al. 2004; Mansour et al. 2005; Meira-Lima et al. 2005), *GRK3* (22q12.1) (Zhou et al. 2008; Rao et al. 2009) and *COMT* (22q11) (Prata et al. 2006; Burdick et al. 2007; Zhang et al. 2009) have been proposed on the basis of linkage and association studies but replication has been difficult in most cases (Badner and Gershon 2002; Segurado et al. 2003). Possible reasons might be the complexity of the illness as well as the genetic overlap with other psychiatric disorders. Moreover, genes interact, a phenomenon named epistasis, making studies of gene × environment interaction even more complex (LaPorte et al. 2010). The Genome Wide Association Studies (GWAS) published last year have found that *ZNF804A* and *CACNA1C* are over-represented in bipolar disorder (Craddock et al. 2009; O'Donovan et al. 2009).
Phenotypes of Bipolar disorder and genes

Some symptoms at the phenotype level associated with bipolar disorder are reported to aggregate in families, for example lithium response, rapid cycling and early age at onset. These findings support the hypothesis that several genes and genetic mechanisms in combination produce different symptom patterns of the disease. For these reasons, it might be fruitful to study the association of different phenotypes with candidate genes (Craddock et al. 2009). Some studies using this strategy have already shown an association between specific loci and symptoms e.g. lithium response with a specific chromosomal region at locus 10p15 (Perlis et al. 2009), persecutory delusions as well as an early onset with the DAOA gene (Schulze et al. 2005; Gomez et al. 2008), and mood incongruent psychotic symptoms with the loci 1q32.3 and 20q13.31 (Hamshere et al. 2009; Hamshere et al. 2009). There is a need for larger and phenotypically well-characterized patient samples to improve the possibilities of discovering valid associations (Craddock and Sklar 2009).

Courses of Bipolar disorder

Recurrence risk

There is a life-long risk of recurrence in all affective illnesses, especially bipolar disorder, where the number of episodes averages 0.4-1.1 per year. Most of the patients hospitalized in their first manic episode achieve symptomatic recovery within a few weeks but many of them are still functionally impaired for a long period of time, and several patients have relapses in new affective episodes within a short time (Tohen et al. 2003). Nearly half the patients first admitted for mania or mixed episodes have their second admission within 5 years (Paper II). There is a slightly higher recurrence risk for bipolar disorder type 2 patients than for type 1 patients, without gender differences (Angst et al. 2003). The symptom-free periods tend to become shorter with time, and the episodes become longer and more difficult to treat (Marneros et al. 1991; Marneros 1999; Angst and Sellaro 2000).
Problems in making an early diagnosis

The initial affective polarity in bipolar patients is most often depression, and for this reason it is often difficult during the early phase of the illness to differentiate between Major Depressive disorder (MDD) and Bipolar disorder. However, this distinction must be made as early as possible, for the simple reason that the treatments are different. In bipolar disorder, mood stabilizers should be started early, whereas antidepressants should be largely avoided in mono-therapy in order to reduce the risk of a switch into mania (Post et al. 2001; Licht et al. 2008). Further, a correct diagnosis and treatment are of highest importance considering the psychological, social and economic consequences of every single episode (Baldessarini et al. 2007).

Rapid cycling

About one fifth (12-24%) of the patients with bipolar disorder suffer from a more severe course, defined in DSM-IV by four or more episodes within a year, as rapid cycling (Calabrese et al. 2001; Kupka et al. 2003) occurring in both bipolar disorder types 1 and 2. This variant of severe illness has been associated with a poorer outcome with a higher risk for suicide attempts and a higher rate of alcohol abuse. The etiology is still being discussed, and studies over the past 30 years have failed to establish rapid cycling as a special subgroup of bipolar disorder. An early age at onset, an episode pattern where a depression commonly comes before a mania, i.e. Depression-Mania-Free Interval course (DMI), rather than a Mania-Depression-Free Interval (MDI) course, and treatment with antidepressants as well as hereditary factors might be important predictors for rapid cycling. However, all these predictive findings are inconsistent and the only predictor consistently evident is a female preponderance. There might be a family aggregation of rapid cycling, but studies have failed to identify this (Fisfalen et al. 2005; Bauer et al. 2008). Using molecular genetics, previous studies have proposed candidate genes such as COMT (Kirov et al. 1998), 5-HTTLPR (Rousseva et al. 2003) and BPNF (Green et al. 2006; Muller et al. 2006) as being associated with rapid cycling in BP, but these findings are also inconsistent and require replication (Bauer et al. 2008).
Previously discussed predictors of a more severe course

Genetic factors

The pathogenesis of bipolar disorder is still poorly understood but there is evidence of a genetic risk contributing to the development of bipolar illness (Craddock and Sklar 2009). Moreover, there are also investigations showing a family aggregation of a more severe course of bipolar disorder (Tsuang and Faraone 1990; Alda 2001; Craddock 2001; Craddock and Jones 2001; McGuffin et al. 2003).

Age at onset

The average age at onset varies between 20 and 25 years according to how the first episode is defined, but the majority makes their debut before the age of 25. Bipolar disorder type 1 patients have their first episode on average about 5 years earlier than type 2 patients (Baldessarini et al. 2010). Onset before 17 years is associated with a more severe course with multiple episodes and a more severe social impairment, and these patients are also more treatment-resistant than others. Some connections have been described between early age at onset and comorbidity, rapid cycling and mixed episodes, but these findings are inconsistent (Goodwin and Jamison 2007).

Delay before maintenance treatment

The average delay between the first symptoms of bipolar disorder and maintenance treatment is in most studies 9.6 years (Baethge et al. 2003). This delay cannot be shown to lead to a more severe course after the start of treatment, but the long untreated period is in most cases associated with social and psychological consequences (Baldessarini et al. 1999; Baethge et al. 2003; Baldessarini et al. 2003; Sharma et al. 2004). Furthermore, there are numerous findings supporting the belief that bipolar disorder is associated with cognitive disturbances and that more episodes before treatment might be a risk factor.
**Personality**

Bipolar disorder patients comorbid with Borderline personality disorders or Substance abuse disorders may have a poorer outcome of treatment, but this area is complex and replete with conflicting findings. Personality may influence the course of the illness by itself, but it may also have an indirect impact by affecting the adherence of treatment (Colom et al. 2000). It has been suggested that borderline personality disorder belongs to the bipolar spectrum but there is insufficient support for this idea, even though the two disorders may share certain etiological factors (Akiskal 2004; Smith et al. 2004; Paris et al. 2007). The ability to cope with stress, and to maintain close relationships and adherence to treatment are all factors predicting a good prognosis (Colom et al. 2005; Post and Leverich 2006).

**Comorbidity with other Axis I disorders**

At least 65% of patients have been reported to have other comorbid lifetime psychiatric axis 1 disorders. The most common are Anxiety disorders, followed by Substance use disorders (Simon et al. 2004). Panic disorder is the most common comorbid anxiety condition, and Alcohol use the most common Substance use disorder (Kessler et al. 2001; McElroy et al. 2001). Bipolar disorder comorbid with anxiety disorders has a more severe course with on average a poorer outcome as social impairment, while bipolar patients with comorbid alcohol substance disorders are more treatment-resistant and have a higher suicide rate (Goldstein et al. 2006; Cardoso et al. 2008).

**Mixed episodes**

Since the 19th century in French and German psychiatry, it is well known that manic and depressive symptoms can often co-occur in the same affective episode. Historically, these episodes have been named, for example, agitated depression and dysphoric mania. The DSM-IV definition of a mixed episode is an episode where the criteria for both depression and mania are met at the same time (Table 1). Clinicians know that mixed episodes are more complex and, in modern terms, the term “mixed” has become popular in situations of two or more symptoms of depression during
a manic episode or at least two manic symptoms in a depressive episode. There is still a debate about the definition of a mixed episode (McElroy 2008), but there is a consensus that bipolar patients with mixed symptoms in episodes are more severely ill than others. The suicide rate is higher, and psychotic features, co-morbidity with other axis I disorders and substance misuse are commonly present (Freeman and McElroy 1999; Goldberg and McElroy 2007; Azorin et al. 2009). The frequency of patients with mixed episodes, according to the clinical definition, is about 20% in bipolar patients, and there are suggestions of a gender difference with a larger proportion of women suffering from this form of episodes (Suppes et al. 2005; Kessing 2008).

**Psychotic features in Bipolar disorder**

Psychotic symptoms are common in bipolar episodes. These symptoms are usually in line with the level of mood, i.e. mood-congruent. Psychotic symptoms not in line with the prevailing mood, called mood-incongruent, can however also occur. The illness is classified as Schizoaffective if two or more clearly psychotic symptoms are presented in the absence of distinct affective episodes for at least 14 days (DSM-IV). There is no evidence that mood-congruent psychotic symptoms are associated with a more severe outcome (Keck et al. 2003).

**Cognitive impairment in Bipolar disorder**

**Cognitive symptoms between episodes**

Evidence of cognitive impairment in bipolar disorder has been obtained by comparison with controls matched for a similar education level (Bearden et al. 2001; Kieseppa et al. 2005). The most consistent cognitive impairment represented in intervals free from manic or depressive symptoms, i.e. euthymic phases, of bipolar patients, is impaired memory and impaired executive functions. Findings of premorbid cognitive impairment are inconsistent.
Several studies have shown a correlation between a severe course of bipolar illness and permanent cognitive impairment, and some authors have reported that multiple episode patients have performed worse on executive functions and have a poorer memory function than others (Martinez-Aran et al. 2000; Cavanagh et al. 2002; Clark et al. 2002; Bearden et al. 2006). However, one limitation of such studies is that most of the investigated bipolar patients are on maintenance treatment, and it is still not known whether the medication influences the cognitive function. Many patients with a severe course are however on multiple drugs, and there will be a relationship between drugs given in high doses and cognitive problems. There are no studies on severely ill patients without medication. The question as to whether the cognitive deficits appear early in the course or are an effect of multiple episodes is also still under discussion (Gruber et al. 2008). The main problem is how to define the onset of bipolar illness since a bipolar diagnosis is not usually established until the first or second mania and a number of depressive episodes (Goodwin et al. 2008).

**Cognitive symptoms during episodes**

Cognitive disturbances in ADHD and bipolar disorder are neuro-physiologically and neuro-chemically well interpreted. In bipolar patients, the cognitive impairment increases over the years whereas in ADHD these problems have commonly been present since early childhood. Besides more permanent cognitive symptoms in bipolar disorder, cognitive symptoms also appear during affective episodes. Cognitive symptoms of mania are concentration disturbances, talkativeness and thought disorder, while common cognitive symptoms of depression are a diminished ability to think, inflexibility and memory dysfunction. In attention and concentration difficulties in mania are short-term working memory dysfunctions, and they are believed to result from noradrenergic and dopaminergic instability (Berk et al. 2007), in contrast to the long-term cognitive disturbances seen in bipolar disorders and ADHD such as impairment of working memory, future planning and flexibility, which are associated with more continuous suboptimal dopaminergic levels in the dorsolateral prefrontal cortex area (DLPFC) (Cools and Robbins 2004; Levy 2009). Four dopaminergic pathways have been described in the human brain the tuberoinfundibular,
nigrostriatal, mesolimbic and mesocortical projections, which modulate impulsivity, attention seeking, reward seeking, working memory, executive functions, and emotional processing (Cousins et al. 2009). Neuroimaging studies of bipolar disorder have shown increasing evidence for mediotemporal abnormalities (enlarged amygdala) as well as prefrontal abnormalities (reduced anterior cingulate gyri), and increased rates of white matter hyperintensities (Brambilla et al. 2005). P2RX7 might be one of the important genes for the central dopamine system. This gene is located in chromosome 12p24 and encodes for P2X7 receptors, which are purinergic L-typed Ca\(^{2+}\) channels with several important effects for neurotransmission, neuromodulation, glial communication and neurotrophic actions. Activation of these channels induces burst firing of dopamine cells (Liu, 2007).

**Maintenance treatment of Bipolar disorder**

**Lithium treatment**

Prophylactic pharmacological treatment is crucial for a good prognosis of bipolar disorder (Baldessarini et al. 1999; Angst et al. 2003; Baldessarini et al. 2003; Maj 2003). Lithium is nowadays accepted as the first-line mood stabilizer and it has also been shown to prevent suicidal behaviour (Tondo and Baldessarini 2009). Further, there is evidence for a neuroprotective effect of lithium (Bauer et al. 2003; Chuang 2004). The mechanism behind lithium efficacy is not yet known, but extensive research is currently in progress to develop neurotrophic drugs useful for the treatment not only of bipolar disorder but also of other neurodegenerative illnesses (Machado-Vieira et al. 2009). The prophylactic drug treatment of bipolar disorder is, however, complex and lots of information must be considered before selecting treatment — such as family factors, the course of the illness, the duration of episodes, psychiatric as well as somatic comorbidity, and side-effects.
**Combination therapy**

Lithium is most effective in the prevention of manic episodes. For the prevention of depressive episodes, combination with antidepressants or lamotrigine is often necessary. Patients with mixed episodes are preferably treated with anticonvulsants and, when rapid switches occur, a combination of lithium and anticonvulsants might be the solution. The use of antidepressants is believed to induce mood switches from depression to manias (Post et al. 2001; Post et al. 2005; Leverich et al. 2006), but these findings are still being discussed. However, most guidelines on bipolar disorder recommend a combination with a mood stabilizer during antidepressant therapy.

**Psychosocial treatment**

Long-term treatment with mood stabilizers is demanding for many patients lacking motivation and/or suffering from pharmacological side effects. Non-adherence is the most important predictor of a recurrent course in bipolar episodes (Schou 1997). Only about half of the maintenance-treatment patients adhere fully, while a quarter adhere partially, and a quarter are non-adherent. Adherence obviously needs to be improved (Sajatovic et al. 2007; Sajatovic et al. 2009). Moreover, in spite of a good maintenance treatment there is always a risk of a relapse in bipolar episodes — most of the bipolar patients and their families need psychotherapeutic, psychoeducative and/or psychosocial interventions (Perry et al. 1999). Cognitive therapy, family-focused therapy and psychoeducation focused on the recognition of early signs of episodes, social rhythms and environmental triggering factors seem to be the most efficacious way to predict recurrences and to hasten recovery in medicated bipolar patients (Colom and Vieta 2004; Miklowitz et al. 2007; Scott et al. 2007).
THE CURRENT PROJECT

Aims

The all-embracing aim of the present project was to try to specify predictors for a more severe course in order to help clinicians to identify patients “at risk” at an earlier stage.

Specific aims:

Study I: to investigate retrospectively a clinical sample as a foundation for future prospective analyses, and to identify possible prognostic predictors with an emphasis on pharmacological treatment. We also wished to test innovative methods for measuring the burden of illness in terms of a combination of the duration and the severity of episodes, and to test the validity of different outcomes.

Study II: to analyze trends in hospital admissions for bipolar disorder in Sweden from 1997 to 2005, specifically addressing first admissions, to calculate readmission rates during a five year follow-up for all patients with their first or second admission for bipolar disorder in the year 2000. Further, we also aimed to estimate the economic impact of hospitalization for bipolar disorder.

Study III: to investigate associations between selected SNPs in previously proposed candidate genes and various mania phenotypes.

Study IV: to investigate an association between the P2RX7 gene and rapid cycling in bipolar disorder.
OVERVIEW OF PATIENTS AND METHODS

Paper I — Identifying predictors for good lithium response

We recruited and investigated 100 bipolar patients from the Clinic for Affective Disorders, Psychiatry Southwest, at the Karolinska University Hospital in Huddinge, Stockholm. We used the lithium monitoring register, and utilized a life-charting methodology (LCM) in making a basic description of the clinical variability of predictors, symptoms and treatments. We tested predictors and outcomes of long-term course according to earlier published data. In addition to the ordinary outcome measures for long-term course, such as the intervals between episodes, the number of episodes per year, part of the time in episodes, we also used a combination of the accumulated duration and severity of episodes measured as functional disability i.e. the “Accumulated Burden of Mood Swings” (ABMS) as described by Ehnvall 2002. We defined a good lithium response as freedom from episodes for at least three years after the start of the lithium maintenance treatment. Further, we tested the importance of different predictors on the lithium response.

The life-charting method

The variability of the long-term course of bipolar disorder was systematically investigated by Emil Kraepelin. In his well known book Manic Depressive Insanity and Paranoia he graphically described the course of bipolar disorder (Kraepelin 1921). LCM has subsequently been revised and used to provide a better descriptive picture of the variability of bipolar disorder by Meyer, Roy Byrne, Denicoff, Post and Leverich (Meyer 1948; Roy-Byrne et al. 1985; Denicoff et al. 1997; Leverich et al. 2001). The Life-charting technique involved was later computerized to give a graphical illustration of life-events, episode frequency and duration, as well as the severity of episodes and treatments. In Sweden, a LCM program based on ideas from Meyer and later Post was developed by Anna Ehnvall (Ehnvall et al. 2003), who also constructed the illness burden measure ABMS. The
method was further developed in our group for prospective life-charting and statistical analysis (Figure 1).

**Fact box 1.**
Classification of episode severity according to DSM-IV symptoms and degree of disability

<table>
<thead>
<tr>
<th>Depression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>2-4 depressive symptoms, no functional impairment</td>
</tr>
<tr>
<td>Moderate</td>
<td>fulfilled symptom criteria, sick leave ≤50%</td>
</tr>
<tr>
<td>Severe</td>
<td>fulfilled symptom criteria, sick leave &gt;50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mania</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>more than 1 symptom for mania, no functional impairment</td>
</tr>
<tr>
<td>Moderate</td>
<td>fulfilled symptom criteria, sick leave ≤50%</td>
</tr>
<tr>
<td>Severe</td>
<td>fulfilled symptom criteria, sick leave &gt;50%</td>
</tr>
</tbody>
</table>

Participants were asked to give detailed information about heredity, socio-demographics, important life-events, affective episodes and treatments during the whole life span. The affective episodes were categorized into three groups according to symptoms and functional disability related to the extent of sick-leave (Fact box 1)(Roy-Byrne et al. 1985). We then complemented the information from medical records (we had copies of almost all medical records, the oldest from 1934). Discrepancies between the information derived from interviews and the medical records were clarified by telephone (Figure 1).
**Figure 1.** Graphic illustration of the course of episodes in relation to different treatments and life events. The horizontal line in the middle is the time axis. The height of the bars represents the severity of affective episodes and the width their duration. The total area represents the “accumulated burden of illness”, in our paper called the Burden of illness. The lines in the upper part of the figure show different treatments. The vertical texts at the bottom indicate different life events, in this case various relationship difficulties and economic problems.

**Statistical analysis**

The LCM computer program was used to create not only individual life-charts but also group statistics. The statistical analyses were performed by SPSS software. Student’s t-test was used to compare the means of continuous variables, chi squared-tests to compare dichotomous variables, and pair-wise t-test comparisons to calculate the effects of lithium usage. Relationships between continuous variables were investigated using
Pearson’s correlation coefficient and multiple and logistic regression to compare the relative influences of different predictors on the effect of the mood stabilizers.

**Paper II — Psychiatric admissions and hospitalization costs in bipolar disorder in Sweden**

The retrospective design, the heterogeneity of bipolar disorder and the small sample were important limitations of the first study. We therefore switched to an investigation of the long-term course of bipolar patients with the most severe course of illness in a larger sample, and we chose an epidemiological approach using the Swedish patient registry, which is run by the National Board of Health and Welfare. This is a nation-wide registry which covers all hospitalisations, date of admissions and up to five diagnoses. We used the first diagnosis according to the ICD-10 diagnostic clusters and selected patients who had their first admission in bipolar episodes (manic F30+F31:0,1,2; depressive F31:3,4,5; mixed F31:6; unspecified/ other episodes F31: 7, 8, 9) during the period 1997-2005, in order to determine whether the proportion of patients with a bipolar diagnosis increased during this period. Further, we focused on the patients who had had their first (n=874) admission for a bipolar episodes during 2000 and followed their readmission rates during a 5 year period. In order to estimate the trends with regard to the annual hospitalization costs for bipolar disorder, subdivided into costs for staff, operation, rents, and overheads, we used the price per bed-day, as estimated by the Swedish Association of Local Authorities and Regions (SALAR), which organizes the health care regions in Sweden.

**Statistical analysis**

The statistical analyses were performed in cohort models, using the SAS package, version 9.1 (SAS Institute, Cary, NC, USA).
Paper III — Cognitive symptoms in mania associated with the P2RX7 gene

Two sets of participants (set 1 n=168 and set 2 n=466 respectively) were recruited from previously diagnosed bipolar patients, most of them from the Clinics for affective disorders, Psychiatry Southwest, at the Karolinska University Hospital, Huddinge and the Northern Stockholm Psychiatry Clinic at St. Göran’s Hospital, Stockholm, with a number from the Lund University Hospital and a few from other psychiatric clinics in Sweden. The bipolar diagnoses were validated by scrutinize the manic symptoms obtained by medical records and interviews focusing on the most severe manic episodes. Phenotypes such as rapid cycling, mixed episodes and the age at onset were assessed. Blood from each individual was collected and prepared for association analysis using allele-specific Taqman MGB probes. Allelic discrimination was performed using the ABI PRISM 7900HT SDS and the SDS 2.2.1 programs. At first we tested 36 SNPs in 8 candidate genes and their association to different symptoms and phenotypes of bipolar disorder in set 1. Preliminary significant associations between cognitive symptoms in mania and SNPs in the P2RX7 gene were further studied in set 2.

Association analysis

A locus is a specific DNA sequence or a gene on a chromosome. An allele is a variant of the DNA sequence at a specific location on a chromosome. A combination of alleles on different locations on a chromosome that are transmitted together is called a haplotype. If the DNA sequence is identical on both homologous chromosomes, the person is said to be homozygous on that locus. If the loci shows allelic variation and the individual carry different alleles on the two chromosomes in the same locus, the person is heterozygous on that locus. It is quite common that one base pair in an allele is replaced by another. If this change has a prevalence of more than 1% is named a Single Nucleotide Polymorphism, SNP (Figure 2).
A base-pair change less common than 1% is called a mutation. Many SNPs have no consequences with regard to symptoms or disorders, but mutations can be ominous. SNPs changing the structure of the protein for which they are encoded are called non-synonymous, while SNPs which do not affect the encoded protein are synonymous. These SNPs can be used as markers and currently more than a million of SNPs are available for researchers. In association analysis, the specific location of genes and SNPs (Figure 3) is identified usually by case-control studies. In our genetic studies (Papers III and IV), we used an alternative method, and compared patients with symptoms or groups of symptoms with patients without those signs, i.e. case-case studies.

Statistical analysis

The statistical analyses for all variables were summarized (mean, standard deviation, range, frequency, Student’s t-test, χ²-test and principal component analysis) using the PASW program v 18.0 (SPSS inc., Chicago, Illinois, USA). The Hardy-Weinberg equilibrium (HWE) was evaluated for each SNP using a chi-squared-test as implemented in PLINK v1.01 (Purcell et al. 2007). Associations between genetic markers and disease status were
analyzed using the UNPHASED 3.0.10 program (Dudbridge 2003). Significant p-values were corrected with permutation tests. For LD analyses, the HaploView software v 4.1 was used. Power was estimated using the Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/).

**Paper IV — The P2RX7 gene modifies the risk for Rapid Cycling in Bipolar disorder patients**

Using a sample where 81 participants had been added to set 2 in Paper III (n=715) we employed the same methods as in the previous study and studied the same 36 SNPs in 8 candidate genes as in set 1. Preliminary significant associations between rapid cycling and four SNPs in P2RX7 were further investigated in set 2 containing the 81 additional patients. We wished to make a more detailed study of the earlier interesting focus in the P2RX7 gene and rapid cycling, and for this reason we added six SNPs in our investigation. We also performed the same association analysis selecting the bipolar disorder type 1 patients only. Calculations were carried out in a case-case manner.

**Statistical analyses**

To increase the sensitivity, since the significance levels were 10 percent (two-tailed) in set 1 due to the small sample of rapid cycling patients. Significance levels chosen were then 5 percent (two-tailed) in set 2 and in the total sample. Significant p-values were corrected with permutation tests. A traditional logarithm of the odds score, LOD was used to assess the linkage between SNPs.

**The LOD score**

The LOD score stands for the logarithm of the odds (to the base 10), and estimates whether two genetic loci are linked together. A positive LOD score favors the presence of a linkage, whereas a negative LOD score indicates
that a linkage is less likely. A LOD score greater than 3.0 corresponds to a 1000:1 odds that the regions are linked (LOD=2; 100:1).

**Ethical considerations**

The Regional Ethical Review Board in Stockholm, Sweden has approved the studies included in this thesis (164/00, 01-389, 02-410).
OVERVIEW OF THE RESULTS AND DISCUSSION

Paper I

In our study the delay before the introduction of lithium treatment was somewhat longer than the average in other modern studies (10.7 vs. 9.6 years) which might be explained by the relatively advanced age of our patients (mean 47, median 49 years), with several participants who had been ill before the beginning of the lithium era. We also found that an onset before the age of 20 was associated with a longer treatment delay (18.1 vs. 10.7 years). Surprisingly, when the duration of free intervals between episodes was tested as an outcome, only small differences were found between our treated patients and earlier samples before the “lithium era”, or those defined as treatment-resistant. The interval between episodes decreased with time (Figure 2). Patients without recurrences are not included for the diagram since they have only a few intervals and only severely ill patients or non-responders were left (after 8 episodes only 70 out of 100 patients left remained).

Figure 2. Duration of subsequent well intervals in four samples of patients with recurrent mood disorder

Duration in Weeks

Well Interval #
We found that the number of episodes, the time in episodes and the “ABMS” decrease after the introduction of a mood stabilizer. The use of a relative measure as the difference or rate between episodes before and after the introduction of a mood stabilizer is misleading since the severity before illness mathematically influences the outcome. In line with earlier studies, a high morbidity before treatment was found to be correlated with a short latency before treatment (Baldessarini et al. 2007). Thus, we found the effect of delay before treatment as a predictor of severity is difficult to investigate.

We defined therefore the outcome of lithium treatment as an absolute measurement and defined two aspects of the outcome; the first was a good vs. bad response, according to the median split of “ABMS” during maintenance treatment, and the second was the absence of any episode during at least three years after the introduction of lithium. We then compared the relative impact of different predictors on the outcome. Rapid cycling (OR=10.7), comorbidity of other axis 1 disorders (OR=3.8) and mixed episodes (OR=2.8) were the most important predictors for a poor outcome of the treatment.

**Paper II**

The increasing number of hospitalizations for patients with bipolar episodes increased during the study period (2000-2005) which might be explained by an increasing awareness of bipolar disorder during these years. The hospitalization costs remained unchanged probably a result of a decreasing length from 33.5 days in 1997 to 29.3 days in 2005. During the whole period, the lengths of manic (29.2 days) and depressive episodes (29.9 days) were similar. However, hospitalizations for mixed episodes were longer, with an average of 42.3 days. Of the 834 patients who had their first admission for bipolar episodes in 2000, 44% had one or more readmissions during the subsequent 5-year period. A small group of bipolar patients (15%) accounted for as much as 66% of the consumed in-patient care. This register-based study is limited by the lack of detailed information of participants.
Papers III and IV

Association analysis testing of 36 SNPs selected from earlier published findings in a limited sample of bipolar patients (n=168), gave three interesting results:

- Cognitive symptoms in mania were associated with the \textit{P2RX7} gene
- Rapid cycling was associated with the \textit{P2RX7} gene
- Mixed episodes were associated with the \textit{G72/30 (DAOA)} gene

These findings were in line with the results described in the first two papers. In attempt to obtain a more detailed view of these associations, we investigated the specific associations of the cognitive impairment in mania and rapid cycling with the \textit{P2RX7} gene (papers III and IV). An analysis of the possible association between mixed episodes and the \textit{G72/30} gene is planned for a future publication.

Paper III

The main finding was an association with the \textit{P2RX7} gene for the cognitive symptoms \textit{distractibility, thought disorder} and \textit{talkativeness in mania} in two independent samples. This is the first finding of an association between specific symptoms in bipolar disorder and this gene.

We demonstrated an association between \textit{distractibility} and the SNP rs1718119 in the \textit{P2RX7} gene (Figure 3). In a principal component analysis, there was a strong correlation between distractibility two other cognitive symptoms in mania — \textit{thought disorder} and \textit{talkativeness}. These three symptoms taken together were even more strongly associated with the SNP rs1718119 (p<0.0006). The \textit{P2RX7} gene encodes for the purinergic P2X7-receptors (Wiley \textit{et al.} 2003; Gu \textit{et al.} 2004). These receptors are members of a family of P2X-receptors activated by extracellular ATP to increase the permeability of the cell membrane to calcium. Dopamine neurons are known to play a central role in cognitive function, e.g. in ADHD, alcohol substance abuse and the permanent cognitive disturbances in bipolar disorder. Our findings support an earlier hypothesis of a pathway from vulnerability in the P2X7-receptors by high intracellular calcium levels to the firing of dopamine...
neurons in the dorsolateral prefrontal cortex and in the dorsal portion of the anterior cingulate cortex areas (Liu et al. 2007). This study is limited by the lack of information about the cognitive state between episodes for these participants, and this might be an interesting field for further research.

Figure 3. The location of the P2RX7 gene on chromosome 12.

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**Paper IV**

In this study, we discovered in our patients an epistasis phenomenon — an interaction between the SNPs rs2230912 in the P2RX7 gene and rs10838524 in the CRY2 gene which is one of the clock genes on chromosome 11, resulting in a more than 7-fold greater risk of developing rapid cycling. The SNP rs2230912, as earlier mentioned, was significantly associated with rapid cycling in set 1. When we focused on the bipolar disorder type 1 individuals, the SNP rs2230912_G allele in the P2RX7 gene showed an association with rapid cycling at the 10% level. This finding was replicated in set 2 and in the total sample (p<0.05). Linkage Disequilibrium (LD) between markers showed that 8 SNPs from rs1718119 to rs1621388 form an LD block (Figure 4). Haplotype associations with these markers showed associations between rs2230911–rs2230912 C-G, including the associated G allele from rs2230912, and rapid cycling. An epistasis test between the associated
rs2230912 in the \textit{P2RX7} gene and the previously associated rs10838524 in the \textit{CRY2} gene revealed in an even stronger association between those two SNPs together and rapid cycling (OR=7.4, p=0.000005).

\textit{Figure 4. The strength of linkage disequilibrium (LD) between pairs of polymorphisms in rapid cycling patients vs. non rapid cycling patients. The heavy-line frame shows a suggested haplotype block, defined with confidence intervals. D' < 1 and LOD < 2 (white) D' < 1 and LOD ≥ 2 (shades of pink/red), D' = 1 and LOD < 2 (blue) D' = 1 and LOD ≥ 2 (bright red).}

This finding suggests that bipolar disorder with rapid cycling is in some way molecularly distinct from bipolar disorder without rapid cycling. Rapid cycling, being a severe form of bipolar disorder, has previously been considered as a categorical entity. Alternatively, the frequency of episodes in bipolar disorders may be considered as a continuum where rapid cycling represents a severe course, which might result from a higher genetic loading. The finding of a more than 7-fold greater risk of developing rapid cycling for bipolar disorder patients with this specific combination of variants of the \textit{P2RX7} and \textit{CRY2} genes might suggest new possibilities of finding diagnostic methods to identify a more severe course of illness.
FINDINGS AND COMMENTS

The heterogeneity of the symptoms and course of bipolar disorder means that large patient samples and detailed research specification of bipolar subgroups are required. The life-charting method is useful in making a graphic overview of the history of individual patients and expedites the collection of group statistics. A limitation is the need for a multitude of data for each participant, which decreases the practical possibility of collecting large samples.

Defining the outcome of the treatment of bipolar disorder as a simple difference or rate between the severity of illness before and after episodes is not feasible. Absolute measurements testing treatment outcome are recommended. The accumulated combination of severity and duration of episodes, i.e. “ABMS” was found to be useful in defining the severity of illness.

Admissions for bipolar disorder are a minor part of all psychiatric hospitalizations. After having their first admission for a bipolar episode, most of the patients are not readmitted within 5 years. However, a small group of bipolar patients consume a large share of hospitalization resources. There is a clinical need to identify these patients in order to individualize their treatment. Patients with rapid cycling, comorbidity for other axis I disorders, or mixed episodes are at risk of a poor outcome, and they may be over-represented among heavy consumers of in-patient care.

Analyzing phenotypic variation — specific symptoms or groups of symptoms — is useful when investigating the association between bipolar genotype and bipolar disorder. The discovery of an association between cognitive symptoms in mania and the P2RX7 gene may open up new possibilities of mapping the neurobiology behind bipolar symptoms, and might lead to new treatment options. The demonstration of how the P2RX7 and the CRY2 genes interact in giving rise to a 7-fold higher risk of developing rapid cycling might give us new diagnostic tools for predicting a malignant course of bipolar disorder.

Associations between genes and clinical pathology at the symptom level might further facilitate the discovery of physiological and neurochemical
mechanisms behind bipolar symptoms. This neurobiological utilization of molecular genetics would offer new tools in diagnosing bipolar disorder as a general disease concept as well as a variety of bipolar subtypes. Future pharmacological treatments especially effective in clinical subtypes of bipolar disorder will depend on this kind of knowledge.
Currently, the cohort of 100 patients has been followed up for more than 6 years. According to the results in paper 2, we plan to investigate if there are any specific characteristics of the group of patients with a high consumption of psychiatric care.

Another planned project is to try to answer the question of whether cognitive symptoms or impairment in free intervals are associated to the \textit{P2RX7} gene, and to investigate whether there are any associations between the \textit{P2RX7} gene and bipolar patients with comorbid ADHD.

In the bipolar gene project, we shall also continue to study the associations between mixed episodes and the \textit{G72/30} gene. Further, we collect are collecting pharmacological data in the genotyped group in order to investigate the association between genes and lithium response. Another project will study the associations between Genome Wide Association Data (GWAS) and clinical phenotypes.
SVENSK SAMMANFATTNING

_Bakgrund:_ Bipolär sjukdom (BP), eller manodepressiv sjukdom är en vanlig och allvarlig psykisk sjukdom. Den klassiska formen med depressioner och fulminanta manier, BP typ 1, förekommer hos 1-1,5 % av befolkningen medan former med lindigare sådana, s.k. hypomanier, BP typ 2 förekommer hos ytterligare 1-2 % av befolkningen. Bländepisoder (ME) med maniska och depressiva symtom samtidigt kan ses vid båda typerna av BP. De flesta som har en bipolär sjukdom tillfrisknar helt mellan sjukdomsepidoderna, men ofta kan kognitiv nedsättning såsom nedsatt arbetsminne, nedsatt planeringsförmåga och stressintolerans kvarstå långt efter det att de akuta sjukdomssymtomen avklungit. Sjukdomens allvarlighetsgrad och behandlingsutfall varierar avsevärt. Tidig och individualiserad behandling är nödvändig för en god prognos. Det är önskvärt men idag mycket svårt att tidigt särskilja de patienter som löper risk att utveckla ett allvarligare sjukdomsförlopp.

_Syfte:_ Att hitta bakgrundsfaktorer som prognostiserar ett mer elakartat sjukdomsförlopp för att tidigt kunna identifiera högriskpatienter och erbjuda dem en individualiserad behandling.

Resultat: Rapid cycling (RC), dvs. fler än tre sjukdomsepisoder under ett år, samsjuklighet för annan psykiatrisk sjukdom eller ME predicerade högre sjuklighet under pågående behandling (Studie I). För de som hade RC var riskökningen nästan 10-faldig. Medelvårdtiderna vid den första sjukhusvistelsen var längre vid ME (42 dagar) än för andra BP episoder (30 dagar). Mindre än hälften av patienterna återintogs vid något tillfälle och endast 15 % av alla patienter stod för 66 % av återintagningarna under 5-årsuppföljningen (Studie II). I genetiska studier fann vi ett samband mellan en variant av genen P2RX7 med dels de kognitiva symtomen distraherbarhet, tankeförloppsstörning och talträngdhet vid manic och dels med rapid cykling. Dessutom var patienter med blandepisoder överrepresenterade i gruppen med en variant av G72/G30 genen. Framför allt fann vi att patienter med en kombination av två särskilda varianter av CRY2- och P2RX7 generna löpte drygt 7 gånger så stor risk att utveckla rapid cycling jämfört med de som inte hade denna kombination (Studie III och IV).

Slutsatser: Life-chartingmetoden är bra för att studera sjukdomsförlopp vid BP, men den tidskrävande processen gör det svårt att insamla större material. Fynden i studien stärker tidigare resultat, där man visat att RC, samsjuklighet med andra psykiska sjukdomar och ME predicerar ett sämre terapisvar. De genetiska fynden är de första som visar ett samband mellan symtom eller fenotyper vid BP och P2RX7 genen och kan bidra till en bättre förståelse för den neurobiologiska bakgrunden till sjukdomen. Upptäckten att bipolära patienter med vissa varianter av generna P2RX7 och CRY 2 i kombination löper en mer än 7-faldigt ökad risk att drabbas av RC, skulle kunna bidra till nya metoder för att identifiera högriskpatienter. Dessa fynd skulle också, i förlängningen, kunna bidra till nya behandlingsmetoder.
ACKNOWLEDGEMENTS

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