Preventive strategies in bipolar disorders: Identifying targets for early intervention


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Preventive strategies in bipolar disorders: identifying targets for early intervention

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Introduction

Intervention in the early phases of mental disorders has become a major clinical and research focus and is one of the main challenges facing contemporary mental health. This growing interest has led to the development of new lines of enquiry as well as the implementation of new types of treatment programme and services. In this context, the early phase of psychosis has attracted considerable attention in recent years; the therapeutic strategies that have been developed as a consequence may be beginning to improve the outcome of these conditions (McGorry & Jackson, 1999). Yet, most of the attention has been directed to schizophrenia, probably in reaction to the pessimism traditionally associated with this disorder (Conus & McGorry, 2002). Bipolar disorders, usually considered with more optimism, have been relatively neglected by this movement in comparison with schizophrenia. However, while Kraepelin’s (1919) initial view of mental illness was excessively pessimistic regarding schizophrenia, it was also excessively optimistic regarding manic depression, and the assumption of a generally good outcome in manic depression has now been challenged many times (Conus et al., 2006a; Coryell et al., 1993; Dion et al., 1988; Harrow et al., 1990; Tohen et al., 1990a, 2000a,b). For the many reasons given in this chapter, it is imperative that a preventive approach should also be extended to bipolar disorders. Indeed, it is likely that the key targets of early intervention in psychosis, namely early detection and optimal, intensive and sustained intervention during the early years of illness, are relevant to bipolar disorders.

Nevertheless, much remains to be explored, and certain basic concepts that are crucial to the development of early intervention need clarification in the context of bipolar disorders. In particular, while the definition of the bipolar spectrum of disorders has received extensive attention (Akiskal, 1999), much less has been achieved in characterizing the various phases leading from the onset of the initial symptoms to the full-blown disorder. Moreover, the study of prodromal manifestations and early phases of bipolar disorders is particularly complex owing to some of the characteristics of the disorder itself.

In this chapter, we review the arguments justifying the development of early intervention in bipolar disorders and then summarize knowledge gathered about the onset of bipolar disorders. We attempt to develop a concept that would facilitate research in this area and provide a basis for a new treatment approach. Importantly, it must be mentioned that ‘early intervention in bipolar disorders’, the focus of this chapter, is distinct from ‘intervention in early-onset bipolar disorders’. The latter group form a controversial subset of bipolar disorders with onsets during childhood. They may also justify specific treatment strategies, but they will not be discussed here.

Rationale for early intervention in bipolar disorders

Until recently, it was considered that bipolar disorders were characterized not only by their cyclic nature but also by full recovery between acute episodes,
and globally by a rather favourable outcome. Many relatively recent publications have come to challenge this assumption for an important subset of patients (Coryell et al., 1993; Dion et al., 1988; Harrow et al., 1990; Tsuang, Woolson & Fleming, 1979; Tohen et al., 1990a). Various factors have contributed to the development of a more realistic view of bipolar disorders. One of them is the development of a more critical exploration of outcome (Table 13.1). While most studies have focused on the observation of the relatively rapid disappearance of manic symptoms, Tsuang et al. (1979) were among the first to observe that 24% of patients failed to return to work for up to 30 years after the first manic episode. Similarly, Dion et al. (1988) observed 44 patients: while 35 (80%) had no manic symptoms 6 months after hospitalization for a manic episode, only 19 (43%) had a job, and only 9 (21%) worked at their level of premorbid competence. Such a discrepancy between syndromal and functional outcome has been replicated many times since (Coryell et al., 1993; Harrow et al., 1990; Keck et al., 1998; Strakowski et al., 1998; Tohen et al., 1990a, 2000a). However, it should be mentioned that most of these studies were conducted in private clinics and, therefore, in selected populations, which do not include more ill and refractory individuals. Follow-up studies in broader, more naturalistic and representative samples are needed to confirm if these findings are generally applicable.

Very few studies have explored outcome after a first manic episode. All of them outline a similar discrepancy between syndromal remission (not meeting criteria for a manic syndrome according to the Diagnostic and Statistical Manual of Mental

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<th>Table 13.1. Outcome after a manic episode in multiple and first-episode mania</th>
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<td>Source</td>
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<td>Multi-episode mania</td>
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<td>First-episode mania</td>
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<td>Conus et al., 2006a</td>
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Disorders, 4th edn (DSM-IV; APA, 1994) criteria), symptomatic remission (absence of significant symptoms) and functional recovery (return to premorbid level of functioning). For example, Tohen et al. (2000a), in the frame of the McLean–Harvard First Episode Project, have explored outcome after a first manic episode. They found that only 33% of patients had returned to their previous functional level 6 months after a first manic episode, although 86% had recovered from the manic syndrome (Tohen et al., 2000a). At 24 months after the initial manic episode, while 98% had fully recovered from the manic syndrome, only 40% met the criteria for functional recovery (Tohen et al., 2000b). These data confirmed previous results (Dion et al., 1988; Strakowski et al., 1998; Tohen et al., 1990b, 1992). A recent analysis of the outcome of bipolar patients treated for a first manic episode at the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne, Australia, between 1989 and 1997 showed similar results, in that 90% of patients achieved syndromal remission at 6 and 12 months but 40% did not meet symptomatic remission criteria at these points, mainly because of a host of anxiety and depressive features (Conus et al., 2006a). Moreover, 66% of patients at 6 months and 61% of patients at 12 months failed to return to previous levels of functioning. Shorter duration of untreated psychosis predicted better symptomatic outcome, while younger age at intake, family history of affective disorder, illicit drug use and absence of functional recovery at 6 months predicted poorer functional outcome at 12 months (Conus et al., 2006a). These results are in keeping with data from Tohen et al. (1990b) and Coryell et al. (1993), who showed that psychosocial impairment extends to all areas of functioning.

It should be mentioned, however, that various factors, such as increased prevalence of substance abuse and a possible deleterious effect of certain forms of pharmacological treatment, may have induced a deterioration in the outcome of mania over the last century (Zarate et al., 2000). It appears that the prescription of antidepressants has contributed to an increase in manic relapses (Angst, 1985) and rapid cycling (Goodwin & Jamison, 1990). Additionally, excessive prescription of typical neuroleptic drugs appears to be associated with an increased rate of depressive episodes (Kukopulos et al., 1980) and poorer functional outcome (Tohen et al., 1990a). It is also possible that living in a more complex society, decreased social support, stigma related to mental illness and high rates of unemployment in certain countries hampers return to work. Finally, in some countries, the process of de-institutionalization, without a corresponding increase in community care, may have an additional role in reducing access to necessary ongoing care.

Nevertheless, the occurrence of such a poor outcome after a first manic episode is of significance and establishes the need for development of new treatment strategies. In 1990, Goodwin and Jamison commented that, notwithstanding difficulties in distinguishing early signs of the illness from ‘normal’ manifestation of adolescence, attempting to identify these signs was of paramount importance considering the potential beneficial impact of an early start of treatment on later outcome. Certain treatment principles developed in the frame of early intervention in psychotic disorders seem to have the potential to bring us a little closer to this ideal. It is, therefore, important to determine if targets identified in early psychosis are relevant to bipolar illness and can be adapted to the treatment of these disorders.

Are targets for early intervention in psychotic disorders relevant to bipolar disorders?

Early intervention in psychosis has two main objectives: (1) to decrease the delay to initiation of treatment (through early detection and engagement of new patients, and if possible detection of high-risk individuals in order to provide preventive treatment) and (2) to provide optimal and specific management for this early phase of the illness. There are some data to indicate that these objectives may have equal applicability to bipolar disorders, and that patients may benefit from treatments based on similar principles. These arguments are discussed in the following sections.
Section 5: The first episode

Need for early detection of new cases: treatment delay in bipolar disorders

The occurrence of a long delay between the onset of psychotic symptoms and the start of treatment in psychosis, and its implications, have been discussed in detail in Chs. 8–10. Strategies to overcome this hurdle and their efficacy have also been described in these chapters. Various studies on bipolar disorders converge to show that, on average, there is a very long delay between the onset of the illness and the time when adequate levels of care are given (Baethege et al., 2003; Egeland et al., 1987; Post et al., 2003). For example, Post et al. (2003, p. 317) reported an ‘average of 10 years between first symptoms meeting diagnostic threshold and first treatment’, and Baethege et al. (2003) found an average mean latency of 9.3 years between first medical contact for the mood disorder and the commencement of treatment with a mood stabilizer.

Various factors can be responsible for such a delay in diagnosing bipolar disorders. First, the index episode of illness is depressive in the majority of patients, and, as a consequence, the most common initial diagnosis is of unipolar depression (Lish et al., 1994). Second, because of the often atypical clinical presentation of mania (high rate of mixed episodes, presence of irritability and flight of ideas rather than the typical euphoria and grandiosity, high rate of psychotic symptoms and comorbidities), many professionals fail to identify mania in adolescents and young adults (Joyce, 1984). Third, hypomania is often pleasant and not associated with impairment and, therefore, not mentioned by patients (Berk et al., 2006). Fourth, the presence of substance-abuse comorbidity may deflect diagnostic attention (Berk et al., 2006). Finally, delay is sometimes not linked to failed diagnosis but rather to patients’ reluctance to ask for mental healthcare. For example, ten Have et al. (2002), in the Netherlands Mental Health Survey and Incidence Study on bipolar disorders in the Dutch general population, observed that only 4 out of 10 patients with bipolar disorder had contacted mental health services in order to receive care. Moreover, a large percentage of those who established contact with mental health services did not present complaints related to their bipolar disorder, an observation already made by Lish et al. (1994).

Case vignette

John was 14 when his teachers began to complain about his disruptive behaviour. He had started skipping school and smoking cannabis and his parents noticed periods of irritability when he was going out all night with his friends, and others where he withdrew and avoided contact. When he was 17, he was admitted for the first time to hospital after a week of sleepless nights where he was smoking a lot, listening to loud music and speaking to himself in his room. He was very agitated and convinced his mind was controlled by aliens who wanted him to fulfil a special mission. He was diagnosed with a first episode of psychosis, recovered quickly from his psychotic symptoms and was discharged with a neuroleptic treatment that he stopped a week after discharge. Between 17 and 21 years of age, he was admitted four times with a similar clinical presentation and was diagnosed with schizophrenia. During his sixth admission when he was 22, clinicians realized that the successive periods of irritability and withdrawal corresponded to manic and depressive phases of a bipolar disorder; a mood stabilizer was introduced, and since then John has begun to progress towards stability.

Consequences of delayed diagnosis

First, some authors have suggested that there may be a reduction in the effect of lithium with increasing delay between onset of the disorder and the instigation of medication (Post et al., 2003). This issue is still debated, however, since other authors have failed to find such an association (Baethege et al., 2003; Baldessarini, Tondo & Hennen, 2003). Whatever the case may be, most authors agree that delay in treatment is linked to poorer social adjustment, a higher number of hospitalizations (Goldberg & Ernst, 2002), increased risk of suicide, development of comorbidities, forensic complications and global impairment of the capacity to face developmental tasks (Conus & McGorry, 2002). Second, increasing numbers of episodes are also associated with a shortening of the frequency of the cycle (Angst, Felder & Lohmeyer, 1980; Roy-Byrne et al., 1985; Zis et al., 1980). This may be linked to Post’s (1992) neurosensitization model, which suggests that an increasing number of relapses produces not only acute modifications but also more permanent alterations in neuronal activity, possibly transduced at the level of gene
expression. These alterations, in turn, might induce a higher tendency to relapse, and possibly a poorer response to medication. Third, delayed identification of bipolar disorder and misdiagnosis with unipolar depression can lead to the prescription of antidepressant therapy, which can induce rapid cycling, mania, mixed states and treatment resistance (Ghaemi, Ko & Goodwin, 2002). Fourth, misdiagnosis may also lead to inadequate psychoeducation, inappropriate medication regimens (which, in turn, may have a negative effect on outcome) and rejection from clinicians when symptoms are mislabelled as behavioural issues. Finally, untreated illness may interfere with the attainment of age-specific social, psychological and educational developmental goals (Macneil, 2004).

Optimal treatment of the first episode: are there specific treatment guidelines for the early phase of bipolar disorders?

As Malla and Norman (2001) pointed out, early intervention is not only about intervening early; it should also involve the development of specific treatment strategies. Recent developments in early intervention strategies have revealed the need for specific pharmacological guidelines. For example, it has been shown that lower doses of antipsychotic medication have similar efficacy but a much lower risk of side effects in early psychosis than doses usually prescribed to patients with more chronic disorders (Malla & Norman, 2001; Remington, Kapur & Zipursky, 1998). Additionally, in order to improve outcome, first-episode patients need specific psychological treatment programmes geared towards not only the phase of illness but also the stage of psychosocial development and its associated needs and difficulties (Macneil, 2004).

Current guidelines

Current treatment strategies for bipolar disorders have been developed mainly on the basis of studies conducted in populations of patients with chronic disorder (APA, 2002). Unlike in other medical disciplines such as oncology, psychiatry generally does not use staging models to delineate phase-specific treatment needs. To our knowledge, none of the official guidelines for treatment of bipolar disorders makes mention of specific strategies for the early phase of the illness, neither concerning medication nor regarding psychological approaches (Conus, Berk & McGorry, 2006b). The only guideline elements that can be derived from the most recent version of the Practice Guidelines for the Treatment of Patients with Bipolar Disorder, published by the American Psychiatric Association (APA, 2002) and that can apply to the early phase of bipolar disorders can be summarized as follows.

1. Mood stabilizers (lithium or valproate) should be used during the acute manic phase and continued for at least 6 months after a single manic episode, or 18 months in children and adolescents.

2. Antipsychotic medication should be used in association with mood stabilizers according to the severity of the episode and/or the presence of psychotic symptoms.

3. When entering the maintenance phase of the treatment, need for ongoing antipsychotic medication should be reassessed. Although atypical antipsychotic drugs are sometimes considered for maintenance therapy, definitive evidence that their efficacy as maintenance treatment is comparable to that of lithium or valproate is still missing.

It is worth noting that this last recommendation is likely to change given the recent publication of evidence that atypicals indeed do have maintenance efficacy. For example, olanzapine has been shown to have comparable efficacy to lithium (Tohen et al., 2005), and has been reported to be superior to placebo in prevention of mania, depression and overall relapse in randomised designs (Tohen et al., 2003a,b, 2004).

In addition, a few recent publications have proposed guidelines for the treatment of first-episode psychosis but some of the proposed strategies still need to be studied in the frame of randomized controlled trials (Lambert et al., 2003; National Early Psychosis Project, 1998; Royal Australian and New Zealand College of Psychiatrists, 2005; International Early Psychosis Association Writing Group, 2005). The guidelines published by the Canadian Network for Mood and Anxiety Treatments (Yatham et al., 2005) provide more
up-to-date information regarding issues such as the role of atypical antipsychotic medication in the acute and maintenance phases. Nevertheless, they also fail to address the issues specifically related to the early phase of the disorder.

Current practice

These limited guidelines do not seem to reflect current practice for the treatment of first-episode mania, principally regarding the use of antipsychotic medication. Despite the availability of benzodiazepines to help to control agitation in the acute phase, and regardless of the above-mentioned recommendation that antipsychotic drugs should be used only during acute manic phases with psychotic features, or in particularly severe manic or mixed episodes, antipsychotic drugs remain the most commonly prescribed adjunctive treatment for mania (Conus & McGorry, 2002). Zarate et al. (2000) found that patients with first-episode mania were as likely as those with first-episode non-affective psychosis to receive antipsychotic drugs, although usually at lower dosage. Moreover, they found that 77% of these patients with first-episode mania received antipsychotic medication at discharge and 25% were still receiving it at the 6-month follow-up. In populations with chronic disorder and 6 months after hospitalization for a manic episode, 68% to 95% of patients who have been prescribed antipsychotic drugs are still taking them, and usage in up to 67% has been observed during the maintenance phase (Sernyak et al., 1994; Verdoux et al., 1996). This is a matter of concern for various reasons. First, bipolar patients have a high susceptibility to tardive dyskinesia if they take typical antipsychotic drugs (Keck, McElroy & Strakowski, 2000). Second, if these drugs rather than benzodiazepines are used for acute control of behaviour, they tend to be prescribed at high dosages and this can induce extrapyramidal syndromes and lead to prolonged alienation of patients from treatment. Additionally, Craig et al. (2004) found that patients who were prescribed typical antipsychotic medication ended up with poorer scores on the Global Assessment of Functioning (APA, 1994) at outcome and spent less time in remission. Zarate et al. (2000) also found that prolonged prescription of typical neuroleptic drugs after remission of mania had a detrimental effect (increased risk of side effects, dysphoria, depressive symptoms, shorter time to depressive relapse). Atypical antipsychotic agents constitute a promising alternative to typical neuroleptics for use in acute bipolar mania (Mensink & Sloof, 2004). Their mood-stabilizing capacities still need to be studied (Mahli et al., 2005). Unfortunately, atypical antipsychotic drugs also induce side effects, such as somnolence, hyperprolactinaemia, osteoporosis, dyslipidaemia, weight gain and diabetes, and even extrapyramidal symptoms (Mahli et al., 2005).

Guidelines for prescription of mood stabilizers

Because of the high risk of relapse after a first manic episode and the deleterious effect of multiple episodes on outcome, current guidelines suggest maintenance therapy should be proposed after a first manic episode (Yatham et al., 2005). Additionally, the notion that mood stabilizers have a primary neuroprotective function is gaining currency (Hennion et al., 2002). There is ample neuroimaging data regarding structural changes in bipolar disorder (Monkul, Mahli & Soares, 2005), and recent data suggest that atypical agents prevent structural changes in first-episode psychosis (Lieberman et al., 2005). Similarly, there are data suggesting that lithium and valproate can prevent tissue loss in the amygdala in paediatric bipolar disorders (Chang et al., 2005). If further research confirms these findings, it could strongly support the idea of early initiation of maintenance therapy. However, considering the difficulties most young patients have accepting a diagnosis of bipolar disorder after a first manic episode, the poor adherence rates to lithium in first-episode cohorts and the risk of a rebound episode on abrupt discontinuation, this guideline is often hard to follow in clinical practice.

Treatment adherence

Finally, another dimension of pharmacological treatment, namely adherence to prescribed medication, deserves specific attention. Non-adherence to treatment is known to be an important problem in any medical or psychiatric condition and has been identified as one of the major risk factors for relapse in bipolar disorders.
Basco and Rush (1995) showed that the rate of non-adherence with mood stabilizers was close to 50%. In a cohort of 101 patients hospitalized for acute mania, Keck et al. (1996) demonstrated that 64 (64%) were non-adherent to their medication in the month prior to admission. They also found that treatment adherence was associated with higher rates of recovery and more rapid recovery (Keck et al., 1998). In first-episode patients, the rate of non-adherence seems to be even higher and is reported by some authors to be as high as 57% (Cochran, 1984). Among the 83 bipolar patients in a cohort of 109 patients with a first episode of an affective disorder, Strakowski et al. (1998) reported that 41% were fully adherent, 26% partially and 33% totally non-adherent. Craig et al. (2004) found that 43% of patients were non-adherent to mood stabilizers at 6 months. These numbers might be explained by various factors. First, denial is an associated feature of the illness. It is common for individuals to have a number of episodes before accepting the implications of the recurrent nature of the illness. Furthermore, lifestyle change involved in taking prophylactic medication represents a major challenge, especially for young people. This underlines the need to develop psychosocial interventions aimed at the specific needs of this group of individuals (Macneil, 2004). The impact of non-adherence on outcome of first-episode mania has not been well studied. Strakowski et al. (1998) found that syndromal recovery was more likely to occur for patients with full adherence than for those with partial adherence. The impact of total non-adherence is more difficult to assess because non-adherent patients tend to drop out of research studies altogether. Moreover, non-adherence rarely occurs in isolation and is often combined with other poor prognostic factors such as substance abuse, and might then have an indirect as well as a direct effect on outcome. It is, however, possible that adherence may be a marker of other behaviours or illness characteristics modulating outcome.

Case vignette

Amanda was admitted for the first time when she was 19 years old. She had become progressively agitated and restless over the last month, and hardly slept more than 3 hours a night during the few days preceding admission. She was spending most evenings going out partying without experiencing any feelings of tiredness. On the day of admission, she got into an argument in a shop after she had tried on clothes for more than 2 hours and pretended to leave with various items without paying. On the ward she was over-familiar with the nursing staff, disinhibited and irritable, and her thoughts were accelerated. After long negotiations, she finally accepted medication and was given benzodiazepine first and then sodium valproate. While manic symptoms decreased, she agreed she had gotten carried away at some point but rejected the idea of having had a manic episode. She said she was feeling better than ever and that she had finally overcome her shyness. After discharge, she rapidly discontinued medication, and told her case manager that it made her feel depressed and tired. She also said she missed the time when she was feeling high, and she minimized her disturbed behaviour before admission.

Defining targets for early intervention in bipolar disorders

Based on the previous two sections, it seems clear that early intervention strategies are justified in the treatment of bipolar disorders. However, as mentioned, one of the main challenges in the development of such strategies is to formulate a better definition of the various stages of the disorder, which leads from a vulnerability status to the initial onset-phase and then to the full-blown disorder. The task is made difficult by the nature of the disorder and its cyclical aspects. First, the initial manifestation of bipolar disorders can take many shapes, ranging most commonly from depressive episodes of varying intensity to mania of abrupt onset, both of which can be very hard to diagnose (Berk et al., 2006). In many other cases, onset may be much less clear-cut and manifest as ill-defined mood disturbances. Even though the sensitivity of such symptoms may be significant, their specificity is very low, and they may be very hard to distinguish from manifestations of early adolescence, normal reactions to life events, or early signs of other disorders.

Therefore, one of the main challenges is to diagnose these initial manifestations properly in order to determine which one will eventually lead towards bipolar disorder and, thus, to initiate proper treatment as soon
as possible. In this context it may prove useful to apply a combined strategy: (1) to develop a better characterization of the signature of bipolar depression, allowing prospective identification of bipolarity in individuals presenting with depression; (2) to gather more extensive knowledge about initial manic manifestations of the disorder; and (3) to explore and define the more progressive forms of onset, which by analogy with early psychosis could be defined as the ‘initial prodrome’ to bipolar disorder.

**Bipolar depression**

As discussed above, depression is the most common type of onset in bipolar I patients (Perugi et al., 2000). Additionally, in bipolar disorder, the bulk of morbidity is in the depressive phase of the disorder. Finally, the ratio of depressive to manic episodes in bipolar I disorder is 3:1, whereas in bipolar II disorder the ratio of depression to hypomania is 47:1 (Judd et al., 2002). This creates a scenario where young people with developing bipolar disorder present with depression and are inevitably at risk of being misdiagnosed as unipolar. This is a concern, considering that antidepressants can induce mania, mixed states and rapid cycling in susceptible individuals; that antidepressant-induced manias are more likely to be dysphoric than euphoric (Berk & Dodd, 2005); that mania in young people is indeed more likely to be dysphoric (Wozniak, Biederman & Richards., 2001); and finally, that suicidal risk is disproportionately high in mixed states (Berk & Dodd, 2005). For these reasons, the development of strategies allowing an accurate and early diagnosis of bipolarity in depressed young individuals is critical and is an important target for early intervention.

**First-episode mania**

A major reason for latency between onset and treatment in bipolar disorders is the failure to identify mania in young patients, which can be explained by various factors. First, the clinical presentation of mania is frequently atypical in adolescents and young adults, with high rates of mixed episodes, as evidenced by irritability and increase in energy and flight of ideas rather than euphoria and grandiosity (Akiskal et al., 2003; Wozniak et al., 2001). Second, mild mania is uncommonly a source of distress and, therefore, seldom a focus of clinical attention. Third, disruptive behaviour in mania can overlap phenomenologically with personality disorders: symptoms and diagnosis can easily be mistaken for cluster B personality traits and disorders in patients with recurrent and long-standing behavioural disturbances, unstable personal relationships and periodic affective symptoms (Tryer & Brittlebank, 1993). Akiskal (1981) showed that secondary personality dysfunction can develop in the context of prolonged affective disturbances and can be confused with personality disorder. Fourth, there is also a high rate of comorbidity and overlap with manifestations of other disorders, such as attention deficit hyperactivity disorder, anxiety, substance-use disorder and antisocial behaviour (Wozniak et al., 2001). Finally, younger patients present with a higher rate of psychotic symptoms (Joyce, 1984), more often of a mood-incongruent nature (McGlashan, 1988). For example, in a sample of 108 patients with first-episode psychotic mania treated at EPPIC between 1987 and 1995, Conus et al. (2004) found high rates of mood-incongruent psychotic symptoms, persecutory delusions and Schneiderian symptoms, not only in those with a diagnosis of schizoaffective disorder (100%, 86%, and 81%, respectively) but also in those with a diagnosis of bipolar disorder (74%, 69%, and 59%, respectively). Such a presentation leads to a high rate of misdiagnosis, most often with schizophrenia, but also with conduct disorders, attention deficit hyperactivity disorder and antisocial or borderline personality disorders. Clinicians need to be more aware of these elements in order to be able to consider a diagnosis of mania, even if the clinical presentation is not dominated by euphoria and grandiosity; this, in turn, may allow an earlier and more accurate identification of bipolar disorders.

**Initial prodrome to bipolar disorder**

As mentioned above, in many cases it appears that bipolar disorders develop in a progressive manner. As a first step, it might prove useful to apply the concepts
of ‘prodrome’ and ‘onset’ to bipolar disorders as they have been used for psychosis in general and schizophrenia in particular. The ‘prodrome’ can be defined as the period of disturbance that represents a deviation from a person’s previous experience and behaviour, prior to the development of the threshold features of a disorder. By comparison, the ‘onset’ can be more difficult to define in bipolar spectrum disorders. For example, it might become clear only much later and retrospectively that an initial depressive episode was actually the first manifestation of a bipolar I disorder.

As a first approach, it might prove useful to draw an analogy between first-episode mania and first-episode psychosis. The first psychotic episode must occur for the clinician to make the diagnosis of a psychotic disorder (and is absolutely necessary, for example, for schizophrenia to be diagnosed) and gives coherence to earlier manifestations of the illness once they can be put in the context of the prodromal phase. Similarly, the first manic episode marks the diagnosis of a bipolar I disorder. What happens during the pre-manic phase – episodes of sub-threshold or threshold depression, hypomania or anxiety syndromes, for example – could be considered as the initial prodrome to bipolar I disorders and become a key target for early intervention. However, a key challenge is that, as in prodromal schizophrenia, potential early symptoms of bipolar disorder such as depression and anxiety are both widespread and of low specificity. Additionally, they are more likely to follow an intermittent, rather than a continuous, pattern. Mild mania, while specific, is ego-syntonic, rarely distressing and consequently seldom reported. Moreover, such definitions have limitations and are difficult to apply to other disorders of the bipolar spectrum, such as bipolar II disorders. Nevertheless, they might allow the exploration of the initial phase of the illness and be further refined and adapted at a second stage.

Where do we go from here?

In summary, treatment of the early phase of bipolar disorders currently lacks specificity, and most published guidelines fail to differentiate treatment strategies early in the course from those recommended for later stages. The important issues of inaccurate and delayed identification of the disorder, delayed prescription of mood stabilizers, unclear ideal duration of mood-stabilizer treatment, high use of antipsychotic medication and, finally, poor adherence to treatment have been described above. Additionally, there are specific psychological and social issues associated with the onset phase of the disorder that are not specifically addressed by currently available psychological interventions. All these elements suggest there is an urgent need for research and development in early intervention in bipolar disorders. Various strategies that could be applied to face this challenge within the broader framework of early intervention strategies in psychiatry are discussed below.

Earlier identification of bipolar disorders

Earlier identification of the disorder would allow psychological and pharmacological treatment to be commenced sooner, with the potential to reduce the neurobiological and psychosocial collateral damage caused by prolonged duration of untreated illness. Additionally, medication could be introduced in a phase where it may be more efficacious. Two strategies might have an impact on delayed identification of bipolar disorders: improved identification of first-episode mania and of bipolar depression.

Improved identification of first-episode mania

Mania often has an atypical mixed or dysphoric presentation during adolescence and early adulthood. Clinicians should be more aware of this problem, and replication and extension of studies focusing on the particular clinical presentation of first-episode mania are useful in this regard. However, such studies aiming at identifying and refining the characterization of discrete syndromes have their limitations. As mentioned by McGorry (1995a), current categorical classifications for mental disorders do not fit well with the clinical presentation of initial psychotic disorders; this certainly also applies to affective psychoses and bipolar disorders. It may, therefore, prove useful to develop
diagnostic approaches based on a dimensional concept. In this frame, the ‘affective dimension’ of a clinical presentation may constitute a valid and useful additional target for early intervention.

**Identification of bipolar depression**

There is currently limited knowledge regarding the characteristics of depressive episodes that might presage the future development of bipolar illness. Strober and Carlson (1982) examined a cohort of 60 adolescents with major depression and found that the presence of mood-congruent psychotic features, psychomotor retardation, rapid onset and pharmacologically induced hypomania was associated with a higher risk of developing bipolar illness. More recently, Berk et al. (2004) reviewed the literature relevant to this issue and pointed out the following features of bipolar depression: early age of onset, abrupt onset/offset, psychomotor retardation (altered emotional reactivity, delay in verbal response, slowed movements), melancholic symptoms (worthlessness, unvarying mood, marked anhedonia), atypical depressive symptoms (hypersomnia, hyperphagia, leaden paralysis) and other features such as irritability, mixed states, lability and high level of recurrence. A new Bipolar Depression Rating Scale has been developed that should contribute to resolving this issue (Berk et al., 2007). Screening instruments for hypomania such as the Mood Disorder Questionnaire (Hirschfeld et al., 2003a) would also be a valuable additional component to routine care to detect potential bipolarity in young individuals presenting with depressive symptoms.

**Identification of the initial prodrome to bipolar disorders**

While an important body of literature has been published on the warning signs of manic relapses, the ‘initial prodrome’ to bipolar disorders has received little attention. Various approaches can be proposed to explore this phase of the illness. Akiskal et al. (1985) prospectively followed 68 juvenile offspring or siblings of bipolar patients with mood symptoms. They observed an often insidious onset of bipolar disorder in late childhood, adolescence or early adulthood, with relatively minor oscillations in mood that were mainly depressive in nature. It could be argued, however, that the restriction of the study to offspring of bipolar patients might limit the relevance of the findings to be only applicable for patients with a family history of bipolar disorder, which is not true for all bipolar patients. The most systematic and detailed study of the initial prodrome to bipolar disorder to date comes from Egeland et al. (2000), who as part of a broader Amish study examined medical histories of 58 bipolar I patients. They were able to identify a range of symptoms and behaviours precluding the onset of illness: episodic changes in mood (depressed mood 53%, anger dyscontrol 38%, irritable mood 33%) and energy (increased energy 47%, decreased energy 38%) were the most consistently reported. These were followed by bold/intrusive behaviours (29%), excessive behaviours (28%), conduct problems (28%), decreased sleep (26%), crying (26%) and oversensitivity (24%). The strengths of this study are its inclusion only of patients formally diagnosed with bipolar disorder, and its use of data spontaneously provided during the early phase of illness. However, it is limited by its reliance on file data rather than on a standardized interview, and by the fact that social history was provided by informants rather than by the patients themselves. This may have led to an overemphasis on observable behavioural changes and neglect of depression or more subjective aspects of prodrome and onset. Additionally, the study was conducted within an Amish population; young people who develop bipolar disorders and live in more standard conditions are highly likely to have an added smoke-screen of substance abuse added into the clinical picture, making early diagnosis even more difficult. A study is currently underway at EPPIC that aims to assess retrospectively the 12 months preceding a first manic episode in a cohort with a first episode of bipolar mania, in order to identify possible clinical markers of an at-risk mental state (Conus et al., 2006c).

In contrast to these retrospective studies, Thompson et al. (2003) have provided prospectively collected data about the development of manic episodes in three patients who developed bipolar I or II disorder during their treatment in a clinic specializing in patients at
ultra high risk of developing psychosis (Yung et al., 2003). A review of the case descriptions reveals that all three patients presented with an initial depressive episode and reported some degree of anxiety and paranoia prior to their inclusion in the clinic. Other symptoms that either emerged or were evident during the three patients’ 12 months of treatment included mood swings (in two), racing thoughts (in two), increased activity/energy (in two), decreased energy/tiredness (in two), disturbed sleep (in two), distractibility/difficulty concentrating (in two), and perceptual changes (in two). A range of comorbid diagnoses were also present. These symptoms are generally in keeping with those of the retrospective reports (Egeland et al., 2000) but it is important to note that there were no specific prodromal features that clearly distinguished patients who developed bipolar disorder from those who developed other psychoses such as schizophrenia.

Other limitations of this study include its very small sample size and its focus on early psychosis rather than exclusively on bipolar disorders, which implies the use of assessment tools that may not have been specific enough to capture various aspects of the pre-manic mood prodrome.

It is important to note that this approach, as well as the methods used in studies mentioned above, have important limitations; for example, none of them used a matched control group of participants who do not go on to develop bipolar disorder, and there are problems with retrospective recall as it introduces subjective bias and also relies upon the patient’s memory. Additionally, Bellivier et al. (2003) demonstrated in a consecutive series of 368 patients that it is possible to differentiate, based on the age of onset, three subgroups of bipolar disorders: (1) an early age of onset group (mean age 17.4 years), (2) those with a medium age of onset (mean age 25.1 years), and (3) those with late age of onset (mean age 40.4 years). This may further complicate the exploration of the prodromal phase, since it is likely that each of these subgroups go through distinct and specific prodromal phases. For example, it has been shown that the ‘early presentation’ category tends to be associated with early comorbid forms of presentation, higher levels of functional impairments and more frequent psychotic symptoms (Carlson, Bromet & Sievers, 2000). However, despite these difficulties and limitations, these works open a new field of research and pave the way for more sophisticated research protocols. Once potential high-risk profile(s) for bipolar disorders can be defined, the next step would be to explore their validity and specificity in the context of larger prospective high-risk studies.

**Development of specific guidelines for the treatment of the early phase of bipolar disorders**

**Pharmacological treatment**

Pharmaceutical treatment of the early phase of bipolar disorders needs to be more extensively studied in order to develop phase-specific guidelines. Each phase defined above may then constitute a specific stage of the disorder where distinct treatment strategies would apply.

The identification of patients going through a prodromal phase would allow the study of biological events occurring during this critical phase (e.g. modifications of brain structure or gene expression) or the identification of psychosocial factors that might be linked to the emergence and development of the disorder. This, in turn, could lead to the development of potential preventive strategies such as neuroprotective agents, psychosocial interventions or primary prevention of secondary substance-use disorder (Thompson et al., 2003). If identification of bipolar depression can be improved, the issue of initiation of mood stabilizers in young people with a suspected bipolar basis to their depression could be explored. This would contribute to avoidance of the risk of development of mixed or dysthmic mania and consequent suicidal tendencies under antidepressant treatment. No such trials have been conducted though they are strongly needed (Baldessarini et al., 2003; Geller et al., 2004). In first-episode mania, it would be useful to compare the efficacy and effectiveness of mood stabilizers as well as to define the ideal duration of prophylaxis after a first manic episode. Studies are needed on antipsychotic treatment (1) to define the need for, and the optimal
duration of, antipsychotic treatment both in psychotic and non-psychotic mania; (2) to compare typical and atypical antipsychotic drugs in terms of safety as well as efficacy; and (3) to compare the efficacy and effectiveness of various atypical antipsychotic drugs in both the acute and the maintenance phases. Regarding this last issue, a file audit study recently conducted at EPPIC explored response to treatment in a non-randomized non-controlled naturalistic setting and showed that olanzapine had a higher efficacy than risperidone in first-episode affective (mainly manic) psychoses, leading to lower scores on the Clinical Global Impression scale (Guy, 1976) at the end of the trial, a higher rate of global improvement on this scale and a higher rate of remission of positive symptoms (Lambert et al., 2005). Similarly, the comparative efficacy and effectiveness of mood stabilizers in this population has not been documented. Finally, it is necessary to examine whether atypical agents or traditional mood stabilizers have neuroprotective properties in first-episode patients. The confirmation of the capacity of such agents to prevent the neurostructural, neurocognitive and functional consequences of illness would indeed constitute a critical element in helping to define when, and for how long, they should be prescribed.

Psychological approaches

It must be emphasized that the treatment of the early phase of bipolar disorders should involve considerably more than providing medication. Indeed, there has been recognition of this by a number of organizations including the British Association of Psychopharmacology, the World Federation of Biological Psychiatry and the American Psychiatric Association (Jones, Sellwood & McGovern, 2005). The 1990 US National Institute of Mental Health (NIMH) report (Prien & Potter, 1990, p. 149) succinctly acknowledged ‘... it is clear that pharmacotherapy alone does not meet the needs of many bipolar patients’.

In recent years, there has been a growth in research on psychological interventions for bipolar disorder. Specifically, recent reviews have found that individual cognitive–behavioural therapy can have an impact on the symptoms of bipolar disorder, medication adherence, social functioning and likelihood of relapse (Gonzalez-Pinto et al., 2004; Huxley, Parikh & Baldessarini, 2000; Jones, 2004; Scott & Gutierrez, 2004). Although none of these studies was designed specifically for a first-episode population, an emphasis on the importance of early intervention is supported by the finding by Scott et al. (2006) in the largest randomized controlled trial of cognitive–behavioural therapy for bipolar disorder to date, which indicated that this approach was more effective for people who had fewer episodes.

However, the population with first-episode bipolar disorder can provide a clinician with a number of challenges as patients often present with poor insight and high rates of comorbidity with alcohol (Conus & McGorry, 2002) and substance use (Ernst & Goldberg, 2004). Therefore, the clinician may face potential engagement difficulties with a first-episode population, which should be addressed before commencing a psychological intervention. It may be that a focus on the person’s explanatory model of their situation, assistance with practical issues (including addressing accommodation, financial and legal issues), and joint goal setting may be required and may assist with enhancing engagement.

Awareness of developmental issues is also essential when providing psychological interventions for people with first-episode bipolar disorder, given that most people develop the disorder in their late teens and early twenties (Burke et al. 1990; Hirschfeld, Lewis & Vornik, 2003b; Lish et al., 1994). Specifically, the clinician should attend to the impact of the disorder on the person’s developmental trajectory, including their ability to develop independence, and should ‘pitch’ information or therapeutic interventions appropriately to the person’s cognitive and emotional level, and involve family members, who may play a considerable role in the person’s life in the treatment process.

It is now commonly accepted that psychoeducation should be regarded as a key element of good practice in the treatment of bipolar disorders. As Colom et al. (2003) showed, psychoeducation prevents relapses and hospital admission in euthymic bipolar patients. Psychoeducation as it is conducted today in bipolar disorder integrates the following elements: early
detection of the illness (Perry et al., 1999), promotion of regular and adequate lifestyles (Frank et al., 1999), the improvement of therapeutic adherence (Scott & Tacchi, 2002) and treatment of symptoms and the resolution of problems (Lam et al., 2003). All of these elements should be integrated in psychoeducation programmes for bipolar disorders.

However, standardized psychoeducation may require modification for working with a first-episode population. Many individuals with first-episode bipolar disorder may be unwilling to accept their diagnosis, and simply distributing pre-packaged handout material without an understanding of the person’s level of insight or an explanatory model may at best be ineffective and at worst damage engagement and the therapeutic relationship, increase likelihood of dropout or lead to catastrophization and over-identification with the disorder. Therefore, it appears that psychoeducation should occur with a strong awareness of what McGorry (1995b, p. 320) referred to as the ‘psychoeducational needs’ of the person, and should involve ‘... the provision of the right kind of information, provided flexibly and sensitively to each individual ’.’

In a cohort of 87 patients with first-episode bipolar mania, 35 (41%) failed to reach symptomatic remission after 12 months despite a generally good syndromic recovery, and only 34 (39%) returned to their premorbid level of functioning (Conus et al., 2006a). Patients who remained symptomatic suffered mainly from anxiety, particularly social phobia and restriction of social interactions. Additionally, a significant proportion of patients abused illicit substances and failed to adhere to medication.

Emphasis on functional recovery needs to address these comorbid difficulties and may also involve practical assistance around social and vocational functioning, including liaison with employment, educational and voluntary services to assist people in returning to their level of premorbid functioning. Planning for returning to work or study, including managing anxiety, discussion around how the person will explain their absence and identifying potential stressors, can be valuable. In addition, encouraging return to regular sleep and activity schedules can be important prior to recommencing work or study, as these are often disrupted by the disorder.

Relapse-prevention work with people in the first episode can be challenging, as lack of insight, denial and minimization may be more likely in this population, than in a population who have experienced multiple episodes. Rather than simple symptom monitoring, which can create unnecessary hypervigilance and ‘false positives’ following a first episode in individuals and their families, attending to the meaning associated with risk of relapse can be a valuable intervention. Specifically, identifying the person’s beliefs about likelihood of relapse, their perceived control over this and the anticipated outcome should a relapse occur can be an extremely useful focus for psychological intervention.

In summary, psychological interventions with first-episode bipolar disorder can include:
- a strong emphasis on engagement and the importance of developing a positive therapeutic relationship, which can be challenging in the first episode
- awareness of the impact of developmental issues on the presentation of the disorder and its treatment
- involving family members where appropriate, given the likely importance of family members for a first-episode population
- psychoeducation, provided with awareness of its potential impact on the person’s sense of self and understanding of the potentially protective nature of denial, and managing this sensitively
- relapse prevention, including discussion of associated affect and the person’s beliefs around the likelihood and potential impact of relapse
- emphasis on functional recovery, given that this has been largely neglected to date.

Conclusions

While confirming the dearth of early-intervention strategies and the absence of guidelines for the treatment of the first stages of bipolar disorders, the arguments developed in this chapter show that the principles guiding the approach of early psychosis may also be relevant to bipolar disorders. Specific targets can be identified that need to be defined more clearly in order to provide a framework for future research trials.
Once initiated, this domain of research would open the door to numerous other areas of investigation (brain structure, cognition, functional neurochemistry and neuroprotection) that could both improve our understanding of the nature of bipolar disorders and lead to the development of new treatment approaches of higher efficacy.

REFERENCES


Chapter 13: Preventive strategies in bipolar disorders


