Prodromes, precipitants, and risk factors for relapse in bipolar disorder

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Abstract

OBJECTIVE: The purpose of this qualitative review is to examine prodromes, precipitants, and risk factors for repeated episodes of mania and depression in bipolar disorder.
METHODS: PubMed, EMBASE, and PsychInfo were searched for "bipolar disorder" in conjunction with: "prodromes", "triggers", and "life change events".
RESULTS: Phenomenology and prevalence of prodromes, precipitants, and risk factors are described, and their therapeutic implications are outlined.
CONCLUSIONS: Most patients with bipolar disorder are able to recognize their prodromes. This ability depends largely on insight. Psychoeducation focused on improving various aspects of insight, including treatment adherence, reduces incidence of relapses in bipolar disorder.

INTRODUCTION

Bipolar disorder (BD) is a lifelong illness marked by high mortality, long-term disability with poor occupational functioning, and fluctuating course characterized by recurrent episodes of mania or depression. Survival analysis of 82 BD outpatients receiving continual maintenance treatment indicated a 73% risk of relapse into mania or depression over 5 years. Of those who relapsed, two-thirds had multiple relapses (Gitlin *et al.* 1995).

Relapses increase suffering of the patients and their families, increase treatment costs because they lead to hospitalizations, and incapacitate the patients, leading to losses of productivity and income, Understanding of antecedents of relapses may inform efforts aimed at their prevention and mitigation. Detection of an early stage of a worsening of the illness may enable therapeutic interventions that prevent the development of a full-blown manic or depressive episode. Signs and symptoms during that early stage are collectively known as *prodromes* (Lam & Wong 1997; 2005). Recognition of the prodromes is critically important for the long-term management of bipolar disorder.

Episodes of illness are sometimes set off by events that act as triggers or *precipitants.* Stressful life event such as death of a relative may, for example, precipitate an episode of depression or mania. Similar events, however, have varying effects in different patients. This variability is due, in part, to the fact that patients differ in their susceptibility to develop an episode. The susceptibility depends on *risk factors* that vary among patients. The purpose of this qualitative review is to examine prodromes, precipitants, and risk factors for repeated episodes

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of mania and depression in BD. Prodromes preceding the development of the first episode are beyond the scope of this review, and are assessed elsewhere (Howes *et al.* 2011).

METHODS

The databases PubMed, EMBASE, and PsychInfo were searched for "bipolar disorder" in conjunction with: "prodromes", "triggers", and "life change events". No language or time constraint was applied. Abstracts or full texts were screened for relevance. This computer search was complemented by bibliographic cross-referencing. References in each publication were manually searched and further papers identified.

RESULTS

1. Prodromes: Definition, phenomenology, prevalence, and duration

Prodromes in BD are defined as "any cognitive, behavioral and affective signs or symptoms that may make patients think they are entering an early stage of an episode "(Lam & Wong 1997). Thus, prodromes represent early warnings of an upcoming episode. The prodromes for manic and depressive episodes are different. The signs and symptoms represent attenuated forms of mania or depression.

Thus, the prodromes of manic episodes consist, to varying degrees, of decreased sleep, more energy, irritability, increased sociability, increased optimism and confidence, racing thoughts, feelings of importance, and decreased concentration (Smith & Tarrier 1992; Molnar *et al.* 1988; Keitner *et al.* 1996; Lam & Wong 1997; Mantere *et al.* 2008; Goossens *et al.* 2010).

The prodromes of depressive episodes include sadness, loss of energy and interest in surroundings, disturbed sleep, low self esteem, negative thinking, loss of concentration, anxiety, and obsessive worries (Smith & Tarrier 1992; Molnar *et al.* 1988; Keitner *et al.* 1996; Lam & Wong 1997; Mantere *et al.* 2008; Goossens *et al.* 2010).

The largest examination of BD prodromes to date was a cross-sectional study of 90 BD I and 101 BD II patients in Finland (Mantere *et al.* 2008). Prodromes were reported by 45.0% of BD I and 50.0% of BD II patients – not a statistically significant difference. The first prodromal symptom was usually mood congruent. The median duration of the prodromes was 30.5 days. The prevalence of reporting prodromes for the manic phase was 55.2%, for the depressive phase 50%, and for the hypomanic phase 34.8%. The differences between prevalences were not statistically significant.

A small prospective study of prodromal symptoms has been published (Altman *et al.* 1992). Estimates of prevalence and duration of BD prodromes in available retrospective studies are presented in Table 1. It can be seen that the results show considerable variation across studies, and the limited data on the duration of prodromes demonstrate large interindividual variance in terms of standard deviations within studies. There are several potential sources of all that variation. All studies in Table 1 are retrospective. Thus, they are subject to distortions involved in imperfect recall. Additionally, the clinical condition of the patients at the time of the interview varied across studies. In one study, "most subjects were euthymic at the time of data collection"(Goossens *et al.* 2010) (p. 1206), but another study interviewed patients "during a sub-acute phase of their illness" (Mantere *et al.* 2008) (p. 367). It is possible that the large difference between the two studies in the proportion of patients able to identify a prodrome (see Table 1) could be due, in part, to impaired recall in more symptomatic patients included in the Mantere study (Mantere *et al.* 2008)

Furthermore, although the open interviews used by most investigators enabled them to obtain interesting individual details including idiosyncratic symptoms, this method impedes comparisons across studies. Several of the studies cross-checked the data obtained in patient interviews with information obtained from relatives (Molnar *et al.* 1988; Keitner *et al.* 1996). This was not done in all patients, and the agreement between these two sources of information was moderate. Patients and their relatives talk about the illness, and any agreement between these sources is thus difficult to interpret as independent validation.

In spite of the methodological problems, important conclusions can be drawn from the existing literature: The signs and symptoms of prodromes for manic and depressive episode represent, for the most part, attenuated forms of mania or depression. At least 50%, and perhaps up to 92% of BD patients are able to identify a prodrome that precedes the onset of a full-blown episode. This proportion appears to be somewhat higher for manic than for depressive episodes. Patients' relatives have demonstrated some capability to recognize a prodrome.

2. Precipitants

Precipitants are triggers or factors that start an episode. The precipitants of manic or hypomanic episodes in the context of BD have been recently reviewed (Proudfoot *et al.* 2011). Typical precipitants of manic or hypomanic episodes include stressful life events, goal-attainment events, expressed emotion, antidepressant medications, disruption of circadian rhythm, seasonality, and childbirth. Some of these precipitants may also trigger a depressive episode.

2.1. Stressful and goal-attainment life events

There is evidence suggesting that stressful life events accumulate in the period preceding the onset of manic and depressive episodes. If that is true, their causal role in triggering the episodes is plausible. Statistically significant accumulation of stressful life events (such as a

Tab. 1. Prevalence and duration of prodromes preceding manic and depressive episodes.

Author, year	Number of patients	Data acquisition	Proportion of patients able to identify a prodrome		Duration of prodrome (days) Means and SD, unless otherwise indicated	
			Manic episode	Depressive episode	Manic episode	Depressive episode
Molnar 1988	20	interview	#	#	20.5±21.3 range 1–84	11.0±8.6 range 2–31
Smith 1992	20	interview	75%	85%	18.8±18.9	28.9±28.2
Keitner 1996	74	Open-ended self-report form	87%	78%	Not reported	Not reported
Lam 1997	40	interview	92%	75%	Not reported	Not reported
Mantere 2008	191	interview	55%	50%	17*	31*
Goosens 2010	111	interview	72%	72%	Not reported	Not reported

Proportions not given, but the lower limit of the range (1 or 2 days) of prodrome duration suggests that some of these patients would have been classified by other authors as reporting no prodrome; * Median

serious traffic accident or death in the family) in the month preceding the episode was observed in a prospective study of a cohort of 62 BD patients who were interviewed at 3 month intervals during a 2 year period. The rates of life events prior to manic and depressive relapses were similar (Hunt *et al.* 1992).

However, another study using identical design (McPherson *et al.* 1993) failed to replicate the results reported by Hunt et al (Hunt *et al.* 1992). The reasons for this failure remain unclear. A small study (N=30) failed to find a relationship between life events and onset of manic episodes (Sclare & Creed 1990). On the other hand, a retrospective study found a relationship between stressful life events and the onset of manic episodes in BD patients. The relationship was particularly strong for events involving a disruption of social rhythm with sleep deprivation (Malkoff-Schwartz *et al.* 2000).

In a prospective study, 125 BD I patients were interviewed monthly for an average of 27 months (Johnson *et al.* 2008). Negative as well as goal-attainment life events were assessed. Examples of negative events included death of a confidant and severe arguments or relationship changes. Examples of goal-attainment life events included acceptance into graduate school, getting married, or getting hired at a new job. Goal-attainment life events predicted increases in manic symptoms. This result extends and replicates a previous smaller study of goal-attainment effect published by the same group (Johnson *et al.* 2000). Negative life events appeared to predict increases in depressive symptoms, but the results were equivocal (Johnson *et al.* 2008).

Thus, the relationship between stressful (negative) life events and the start of manic or depressive episodes of BD remains unclear. One possibility for the contradictory results reported is the presence of at least two confounding factors that were not taken into account in the studies.

First, it is possible that the effect of stressful life events on relapse varies in the course of BD illness. Thus, the events may be important precipitants of early episodes but become less important as the illness progresses on a more autonomous course (Bidzinska 1984; Ambelas 1987; Dunner *et al.* 1979). On the other hand, others failed to confirm this reduction of sensitivity to stress in time (Hammen & Gitlin 1997)

Second, emerging evidence suggests that stressful life events interact with the Val66Met polymorphism (rs6265) in the brain-derived neurotrophic factor gene (BDNF) in their effect on depressive (but not manic) episodes of BD (Hosang *et al.* 2010). This demonstration of a gene x environment interaction implies that the effects of precipitants on the recurrence of BD episodes may be moderated by genomic influences. Such influences could explain why patients differ in their sensitivity to environmental factors, and, in consequence, why studies of the effects of stressful events on recurrence yield contradictory results. Genes and environment should therefore be investigated jointly in future research.

2.2 Disrupted circadian rhythm

A group of researchers measured changes in activity and sleep to study how they related to the course of affective episodes in rapidly cycling patients (Wehr *et al.* 1982). An unexpected finding was that most patients experienced nights with no sleep each time they switched from the depressive to the manic phase of their illness. This naturalistic observation led to experimental studies using sleep deprivation. During a depressive phase, nine rapidly cycling patients were asked to remain awake for 40 hours. Eight switched out of depression, and seven were rated as manic or hypomanic; indicating that sleep loss may trigger switches from depression to mania (Wehr *et al.* 1982).

Sleep deprivation had actually been proposed and used for the treatment of depression a decade before

Wehr's observations described above (Pflug & Tolle 1971; Zimanova & Vojtechovsky 1974). These early treatment results were confirmed in larger samples. Depressed patients with BD (N=206) were treated with three cycles of sleep deprivation, alone or in combination with various medications. A 4.85% switch rate into mania and a 5.83% switch rate into hypomania were observed (Colombo *et al.* 1999). The usefulness of sleep deprivation in the treatment of BD depression was demonstrated in combination with pindolol (Smeraldi *et al.* 1999) and with light therapy (Colombo *et al.* 2000).

While sleep deprivation may cause a switch from depression to mania and can be used to treat BD depression, it can also cause a recurrence of mania. Mania or hypomania was observed to follow various stressful conditions that were associated with loss of sleep (Malkoff-Schwartz *et al.* 2000), driving though the night, being on night call (Wehr *et al.* 1987), or long flights (Jauhar & Weller 1982). On the basis of these observations linking diverse events to sleep loss and ultimately to mania, Wehr proposed a model of sleep reduction as a final common pathway in the genesis of mania (Wehr *et al.* 1987).

2.3 Antidepressant medications

Antidepressant medications, particularly tricyclics, have been known to trigger a switch from depression to mania since their introduction in the 1950s. A large literature investigating this risk has accumulated. A recent meta-analytic review of the problem examined 73 studies involving 114,521 BD and major depressive disorder (MDD) patients who did or did not receive antidepressants (Tondo *et al.* 2010). The overall risk of mania with antidepressants was 12.5%, whereas without antidepressants it was 7.5%. The antidepressant-associated mania was more frequent in BD than MDD, but surprisingly increased *more* in MDD cases. Tricyclics were riskier than serotonin-reuptake inhibitors. Mood stabilizers had limited protective effect against mood elevation during antidepressant treatment.

3. Risks of recurrence

Maintenance treatments reduce the recurrence rates in BD, and non-adherence to treatment is the principal risk factor for the development of a manic or depressive episode (Velligan *et al.* 2009; Gutierrez-Rojas *et al.* 2010). Non-adherence to maintenance treatment is a common problem in BD (Johnson & McFarland 1996; Gonzalez-Pinto *et al.* 2010). Consequences of medication non-adherence were examined during 21-month follow-up in the treatment of bipolar disorder following a manic or mixed episode (Hong *et al.* 2011). Data were taken from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM), which was a prospective, observational study on patient outcomes with a manic/mixed episode in Europe. Of the 1341 patients analyzed, 23.6% were rated non-adherent over 21 months. Non-adherence was significantly associated with increased risk of relapse and recurrence as well as hospitalization and suicide attempts (Hong *et al.* 2011).

Expert consensus identified cognitive problems, lack of insight, and comorbid substance use disorders as principal risk factors for non-adherence (Velligan *et al.* 2009). Regarding cognitive problems and insight, recent evidence indicates that remissions in BD patients are far less complete than previously believed. "Remitted" euthymic bipolar patients have distinct impairments of executive function, verbal memory, and sustained attention, all of which may interfere with organized activity such as regular intake of prescribed medication (Velligan *et al.* 2009). Similarly, insight does not always normalize when patients remit. Impaired insight was observed in 47% of remitted BD I patients (Varga *et al.* 2006). Furthermore, prospective data from a cohort of 1469 BD patients indicated that residual depressive or manic symptoms at recovery were significantly associated with shorter time to depressive recurrence. Residual manic symptoms at recovery were significantly associated with shorter time to manic, hypomanic, or mixed episode recurrence (Perlis *et al.* 2006), Thus, risk of recurrence increases with the presence of residual mood symptoms at initial recovery.

Patient with bipolar disorder suffer from some levels of dissociation (Latalova *et al.* 2011) and this fact may be associated with problems of patients recognize prodromes.

Emerging evidence suggests that genomic factors may influence susceptibility to BD recurrences. Such influence has been demonstrated for a functional polymorphism of the catechol-O-methyltransferase (COMT) gene. A G–A transition (Val158Met, rs4680) influences the enzyme activity, with the Met allele coding for a less active form of the enzyme. Benedetti *et al.* genotyped a sample of 163 BD I patients and found a significant association between homozygosis for the rs4680 COMT Met variant and a reduced recurrence of manic, but not depressive, episodes during the course of the illness. (Benedetti *et al.* 2011a).

Polymorphism of the C (-1019) G 5-HT1A promoter was investigated in 74 consecutively admitted BD patients. Homozygote carriers of the rs6295 G variant reported *less* stressful events before the need for hospitalization for BD. (Benedetti *et al.* 2011b). This finding was interpreted to suggest that the GG homozygotes have a lower resilience to the detrimental effects of stress. Thus, in these homozygotes, it would take less stress to elicit hospitalization than in patients with the other two C (-1019)G 5-HT1A promoter genotypes. Thus, genomic variations influencing dopaminergic (Benedetti *et al.* 2011a) and serotonergic (Benedetti *et al.* 2011b) neurotransmission may influence susceptibility to recurrences in BD.

Numerous additional factors such as various illnesses, aging, postpartum period, and seasonality affect the risk for recurrences of BD. They are beyond the scope of this review.

4. Therapeutic implications of prodromes

Patients with BD who are "less able to recognize and respond to early symptoms of relapse and …. less accepting of medication" are more likely to relapse and be rehospitalized (Joyce 1985). Recognition of symptoms, their attribution to mental illness, and seeking or at least accepting treatment are of course the principal components of insight (David 1990; Amador *et al.* 1993).

The assessment of prodromes depends partly on objective observation (e.g., rate and content of patient's speech), partly on self-assessment. The latter is particularly important since it determines whether a patient will seek help. Self-assessment requires insight. In BD, insight is more impaired during an illness episode than during remission, in mixed than in pure manic episodes, in bipolar II than in bipolar I patients, and in pure mania than in bipolar or unipolar depression. Impaired insight was recorded in BD patients participating in a retrospective study of prodromes, but the insight scale was administered at the time of the interview, not at the time when the patients were experiencing the prodromes (Lam & Wong 1997). A meta-analysis of four longitudinal studies demonstrated that insight in mania is state dependent (Ghaemi & Rosenquist 2004), and the observed state fluctuations of insight suggest that it may be partly impaired during prodromal stages. However, systematic studies of insight during that period are missing.

Psychoeducation is an important therapeutic approach aiming to reduce relapse and rehospitalization in BD patients. Effectiveness of psychoeducation was tested in a study of 120 remitted BD patients who were randomly assigned to receive group psychoeducation or non-structured group meetings (Colom *et al.* 2003). Psychoeducation was focused to a large extent on improving various aspects of insight, including treatment adherence, and it turned out to be significantly superior to the control condition in reducing the number of relapses, increasing time to recurrences, and reducing the number and length of hospitalizations. At the 2-year follow-up, recurrence rates in patients who received psychoeducation and control condition were, respectively, 66.7% and 91.7%; a statistically significant difference.

Teaching patients with BD to identify early symptoms of relapse and seek prompt treatment from health services is an important goal of psychoeducation. A single blind randomized controlled trial was conducted with 69 BD patients who had had a relapse in the previous 12 months. Seven to 12 individual treatment and psychoeducational sessions were conducted in the experimental group. Time to the first manic relapse and the number of manic relapses were significantly reduced by the treatment. There was no effect on depressive relapses (Perry *et al.* 1999). Other psychosocial approaches, at least partly based on improving insight, have also been tested in BD patients (Kemp *et al.* 1996; Scott & Tacchi 2002).

Although all these psychosocial methods showed some success, there seems to be some room for improvement. It is important to realize that some relapses are not due to lack of information, but to cognitive impairments involving memory and attention that interfere with adherence to medication treatment (Lysaker *et al.* 1998). The recurrence rate of 66.7% reported by Colom (Colom *et al.* 2003) could perhaps be further reduced by cognitive rehabilitation.

These considerations seem to suggest that many BD patients would benefit from an additional program that would periodically collect data on their mental status and provide the results immediately to their doctors. If a prodrome is detected, an action could be taken by the doctor without delay. Such a program is already in existence, and, in a pilot study, it has reduced the recurrence rate in schizophrenia (Spaniel *et al.* 2008).

Each participant, a patient and her / his family member enrolled in the program, completes a 10-item Early Warning Signs Questionnaire (EWSQ). Reminder for the completion of the EWSQ is sent weekly by an automated system to the participants' mobile phones as a text message. Individual EWSQ scores are sent by participants back to the program center, again as a text message. If a total EWSQ score exceeds a pre-set score, an automatically generated alert is communicated to the patient's doctor who can then respond (Spaniel *et al.* 2008). This or a similar telemedicine program could be tested in BD patients.

The preliminary results of genomic studies (Hosang *et al.* 2010; Benedetti *et al.* 2011a;b) cannot be used in the treatment of BD patients at this time. However, they point the way to future development of individualized management of this devastating illness.

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