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Journal of Affective Disorders 74 (2003) 209–217

JOURNAL OF AFFECTIVE DISORDERS

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Review

A systematic review of manic and depressive prodromes

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Received 8 April 2002; received in revised form 5 July 2002; accepted 19 July 2002

Abstract

Background: This paper explores whether individuals with a mood disorder can identify the nature and duration of depressive and manic prodromes. *Methods:* Seventy-three publications of prodromal symptoms in bipolar and unipolar disorders were identified by computer searches of seven databases (including MEDLINE and PsycLIT) supplemented by hand searches of journals. Seventeen studies (total sample = 1191 subjects) met criteria for inclusion in a systematic review. *Results:* At least 80% of individuals with a mood disorder can identify one or more prodromal symptoms. There are limited data about unipolar disorders. In bipolar disorders, early symptoms of mania are identified more frequently than early symptoms of depression. The most robust early symptom of mania is sleep disturbance (median prevalence 77%). Early symptoms of depression are inconsistent. The mean length of manic prodromes (>20 days) was consistently reported to be longer than depressive prodromes (<19 days). However, depressive prodromes showed greater inter-individual variation (ranging from 2 to 365 days) in duration than manic prodromes (1–120 days). *Limitations:* Few prospective studies of bipolar, and particularly unipolar disorders have been reported. *Conclusions:* Early symptoms of relapse in affective disorders can be identified. Explanations of the apparent differences in the recognition and length of prodromes between mania and bipolar depression are explored. Further research on duration, sequence of symptom appearance and characteristics of prodromes is warranted to clarify the clinical usefulness of early symptom monitoring.

Keywords: Bipolar disorder; Depressive disorders; Manic depression; Prodromal symptoms

1. Introduction

Prodromes are described as cognitive, affective, and behavioural early symptoms of a disorder that appear before an episode of depression or mania (Altman et al., 1992; Keitner et al., 1996). Fava and Kellner's (1991) review stated that the duration of a prodrome is defined as the interval from the time that the first symptom is recognised to the time when the symptoms of an episode reach maximum severity. Detection of early symptoms could facilitate early intervention to prevent or reduce the impact of relapse on the individual (Joyce, 1985; Molnar et al.,

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0165-0327/03/$ – see front matter
doi:10.1016/S0165-0327(02)00266-5

1988; Smith and Tarrier, 1992; Perry et al., 1995; Basco and Rush, 1996; Lam et al., 1999).

Recent research on psychological interventions for recurrent unipolar and bipolar disorders has utilised the identification and early management of prodromes as a core strategy (Scott, 1995, 2001; Perry et al., 1999; Lam et al., 2001; Katon et al., 2001). Likewise, user groups such as the Manic Depression Fellowship in the UK are trying to teach individuals to identify prodromes in order to employ self-management techniques.

A systematic literature search was conducted to identify what early symptoms of depression and mania have been described; to determine prodrome duration and any differences in duration between depression and mania; and to explore which early warning symptoms are most commonly identified.

2. Methods

A systematic literature review was conducted. All studies investigating early symptoms of relapse in bipolar or unipolar disorder were eligible for inclusion. Computerised databases searched were: MEDLINE (1966 to December 2000); Best Evidence (1991 to present); PsycLIT (1967 to 1990, 1991 to 1999); CINAHL (1982 to 1995, 1996 to December 2000); EMBASE (1980 to December 2000); Cochrane Database of Systematic Reviews (issue 4, 2000); PREMEDLINE (January 19, 2001).

The search used the subject headings [BIPOLAR DISORDER] or [DEPRESSIVE DISORDERS] with: [PRODROMAL] or [PRODROMES] or [PRODROME] or [EARLY WARNING SIGN] or [EARLY SIGNS] or [EARLY SYMPTOMS], and the term [MANIC DEPRESSION] linked to the subject heading [BIPOLAR DISORDER]. On-line abstracts were reviewed and reprints of potentially eligible articles were obtained. A hand search of all references of included journal articles identified further relevant articles. Researchers with an interest in prodromes were also contacted for advice and details of any other articles.

2.1. Data extraction

Two reviewers independently assessed the articles. A structured proforma recorded eligibility and relevant data such as diagnosis, early symptoms identified, and prodrome duration. Exclusion criteria were: (1) early symptoms of first onset of illness; (2) early symptoms of relapse or subsyndromal symptoms associated with sub-optimal lithium levels or discontinuation; (3) no data, preliminary data, or qualitative data; (4) residual symptoms; (5) case reports; and (6) mixed diagnostic samples, which included schizophrenia or other disorders.

Fig. 1 illustrates the article selection process for the review. Electronic searches identified 40 relevant references and a hand search identified a further 33 references. Of these, nine articles were excluded as a

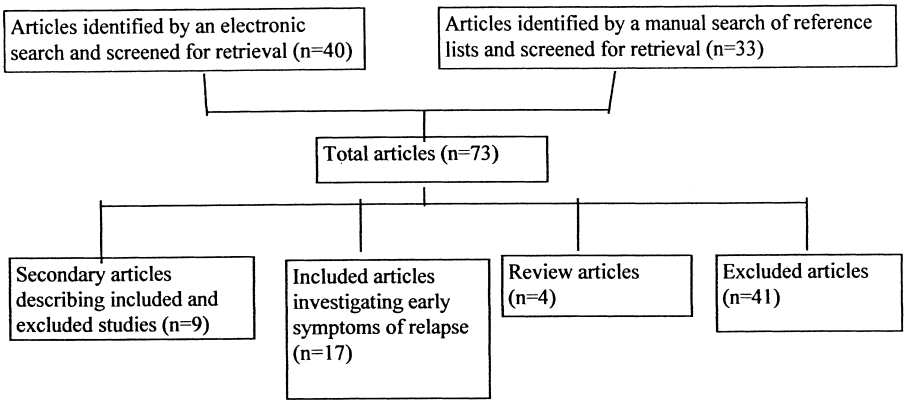

Fig. 1. Flowchart of article selection process.

secondary description of research findings (Sclare and Creed, 1987; Mander and Loudon, 1988; Miklowitz et al., 1988; Roper, 1989; Badal, 1992; Perry et al., 1995; Cates et al., 1999; Nolen, 1999; Lam et al., 2001). Another 41 articles met other exclusion criteria (Table 1). Seventeen studies, published between 1964 and 2001, met inclusion criteria.

3. Results

Demographic data for the 17 included articles is provided in Table 2. Five studies prospectively monitored early symptoms (Post et al., 1981; Altman et al., 1992; Perlis et al., 1997; Perry et al., 1999; Katon et al., 2001). Eleven studies investigated early

Table 1
Studies which met exclusion criteria

Exclusion criteria	Article
Early symptoms of first onset of illness	Hopkinson (1963)
	Hopkinson (1965)
	Winokur (1976)
	Cadoret et al. (1980)
	Murphy et al. (1989)
	Dryman and Eaton (1991)
	Ernst et al. (1992)
	Eaton et al. (1995)
	Strakowski et al. (1995)
	Eaton et al. (1997)
	Judd et al. (1997)
	Rueter et al. (1999)
	Egeland et al. (2000)
Early symptoms of relapse or subsyndromal symptoms associated with sub-optimal lithium levels or discontinuation	Mander (1990)
	Fava (1992)
	Klein et al. (1991)
	Klein et al. (1992)
	Keller et al. (1992)
No data, preliminary data, or qualitative data	Badal (1965)
	Jacobson (1965)
	Kelsey (1967)
	Loeb and Loeb (1987)
	Maj et al. (1992)
	Hagerty et al. (1997)
	Mahnert et al. (1997)
Residual symptoms	Faravelli et al. (1986)
	Fava et al. (1994, 1996, 1998)
	Paykel et al. (1995)
Case report	Stoddard et al. (1977)
	Waters (1979)
	Wehr et al. (1987)
	Wehr (1991)
	Terao (1993)
Sample included schizophrenia or other disorders	Kendler and Hays (1983)
	Fava et al. (1988)
	Subotnik and Nuechterlain (1988)
	Roper (1983)
	Birchwood et al. (1989)
	Beiser et al. (1993)
	Murphy and Moller (1996)
	Bechdolf et al. (1998)
	Novacek and Raskin (1998)

Table 2
Demographic information for studies included in systematic review

Study sample	Article	No.	Mean age	% Male
Bipolar disorders	Altman et al. (1992)	19	24	58
	Molnar et al. (1988)	20	38	45
	Smith and Tarrier (1992)	20	44	45
	Lam and Wong (1997)	40	44	42
	Joyce (1985)	50	35	44
	Perry et al. (1999)	69	45	32
	Keitner et al. (1996)	74	42	47
Mania only	Post et al. (1981)	9	37	44
	Sclare and Creed (1990)	24	41	47
	Francis and Gasparo (1994)	100	38	33
	Wong and Lam (1999)	206	44	40
Unipolar and bipolar disorders	Young and Grabler (1985)	11	median 37	36
Unipolar disorders only	Perlis et al. (1997)	14	38	29
	Fava et al. (1990)	15	45	60
	Young et al. (1991)	53	36	26
	Hays (1964)	81	48	51
	Katon et al. (2001)	386	46	26

symptoms of relapse in bipolar disorder (Joyce, 1985; Molnar et al., 1988; Altman et al., 1992; Smith and Tarrier, 1992; Keitner et al., 1996; Lam and Wong, 1997; Perry et al., 1999) of which four investigated manic early symptoms only (Post et al., 1981; Sclare and Creed, 1990; Francis and Gasparo, 1994; Wong and Lam, 1999). Young and Grabler (1985) investigated early symptoms of relapse in a mixed sample of subjects with unipolar and bipolar disorders. Five studies investigated early symptoms of relapse in unipolar depression (Hays, 1964; Fava et al., 1990; Young et al., 1991; Perlis et al., 1997; Katon et al., 2001).

3.1. Early symptoms of unipolar depression

Fava et al.'s (1990) small-scale study ($n = 15$) reported 100% of individuals could identify early symptoms of unipolar relapse. Sleep disruption was frequently cited as an early symptom, but no prevalence data are reported (Young and Grabler, 1985; Fava et al., 1990; Young et al., 1991; Perlis et al., 1997). Fava et al.'s (1990) study identified that the two most common symptoms of unipolar depression retrospectively identified were generalised anxiety (87%) and irritability (60%).

The duration of the prodromal period for major depression was 7–133 days. In a mixed sample of unipolar and bipolar disorders, the median duration of a depressive prodrome was 28 days (Young and Grabler, 1985). Data from other studies is difficult to interpret as the samples were sub-divided a priori according to clinical characteristics (e.g. Hays, 1964).

3.2. Early symptoms of bipolar depression

Eight studies reported the existence of early symptoms of bipolar depressive relapse (Joyce, 1985; Young and Grabler, 1985; Molnar et al., 1988; Altman et al., 1992; Smith and Tarrier, 1992; Keitner et al., 1996; Lam and Wong, 1997; Perry et al., 1999). The majority of individuals (70–100%; median 82%) can identify early symptoms of bipolar depression. Three studies reported percentages of individuals retrospectively reporting specific early symptoms (Molnar et al., 1988; Smith and Tarrier, 1992; Lam and Wong, 1997). The median prevalence of early symptoms was: mood change (48%), psy-

chomotor change (41%), increased anxiety (36%), appetite change (36%), suicidality (29%), sleep disturbance (24%), and other symptoms (22%). However, no symptom was consistently identified (Table 3).

The duration of the prodromal period for bipolar depression in heterogeneous samples showed considerable variation, ranging between 2 and 365 days (Young and Grabler, 1985; Molnar et al., 1988; Altman et al., 1992; Smith and Tarrier, 1992). In studies comprising only bipolar subjects (Table 4), the mean duration of a depressive prodrome was 11–19 days (Molnar et al., 1988; Smith and Tarrier, 1992).

3.3. Early symptoms of mania

Eleven studies reported the existence of a prodromal period for mania (Post et al., 1981; Joyce, 1985; Molnar et al., 1988; Sclare and Creed, 1990; Altman et al., 1992; Smith and Tarrier, 1992; Francis and Gasparo, 1994; Keitner et al., 1996; Lam and Wong, 1997; Perry et al., 1999; Wong and Lam, 1999). Seventy-five to 100% (median 93%) of

Table 3
Early symptoms identified in bipolar disorder

	Early symptoms	Range of sample size	% of individuals identifying this early symptom	Median (%)
Bipolar depression	Mood change	20–40	10–88	48
	Psychomotor symptoms	20–40	10–86	41
	Increased anxiety	20–40	18–59	36
	Appetite change	20–40	10–53	36
	Suicidal ideas/intent	20	29–64	29
	Sleep disturbance	20–40	17–57	24
	Other	20	14–29	22
Mania	Sleep disturbance	20–206	53–90	77
	Psychotic symptoms	20–206	7–80	47
	Mood change	20–206	14–100	43
	Psychomotor symptoms	20–206	10–100	34
	Other	20	20–35	30
	Appetite change	20–206	12–67	20
	Increased anxiety	20–40	11–20	16

Data from Molnar et al. (1988), Sclare and Creed (1990), Smith and Tarrier (1992), Lam and Wong (1997), Wong and Lam (1999).

Table 4
Estimated duration of prodromes for bipolar depression and mania

	Study	No.	Duration of prodrome (days)	Mean length of prodrome (days)
Bipolar depression	Molnar et al. (1988)	20	2–31	10.96
	Smith and Tarrier (1992)	20	3–365	18.8
	Young and Grabler (1985)	11	7–133	median 28[a]
Mania	Francis and Gasparo (1994)	100	2–112	23
	Sclare and Creed (1990)	24	2–120	median 22
	Molnar et al. (1988)	20	1–83	20.5
	Smith and Tarrier (1992)	20	1–84	28.9

[a] NB Mixed sample of unipolar and bipolar depressive disorders.

individuals were able to identify one or more early symptom of mania (Molnar et al., 1988; Sclare and Creed, 1990; Smith and Tarrier, 1992; Keitner et al., 1996; Lam and Wong, 1997; Perry et al., 1999). Five studies identified the percentage of individuals retrospectively reporting each specific early symptom. As shown in Table 3, the majority identified sleep disturbance as an indicator of manic prodromes. The median prevalence of early symptoms was: sleep disturbance (77%), psychotic symptoms (47%), mood change (43%), psychomotor change (34%), other symptoms (30%), appetite change (20%), and increased anxiety (16%).

The duration of the manic prodrome ranged from 1 to 120 days (Post et al., 1981; Molnar et al., 1988; Sclare and Creed, 1990; Smith and Tarrier, 1992; Francis and Gasparo, 1994). As shown in Table 4, in studies reporting mean and median durations, manic prodromes lasted for: 21–29 days (Molnar et al., 1988; Sclare and Creed, 1990; Francis and Gasparo, 1994; Smith and Tarrier, 1992).

4. Discussion

There are three key issues that arise from this systematic review: the limitations of the current research on affective prodromes, the findings on the nature of manic and depressive prodromes, and the implications for clinical practice and future research.

4.1. Limitations of current research

Less than one in a 1000 papers on the clinical features of affective disorders addresses prodromes. Although the sample reviewed exceeded 1100 subjects, the data on prodromes in unipolar disorder is inadequate. There is marginally more data on bipolar disorders, but findings from these studies are limited by the heterogeneity of the samples and methodologies. Although many studies used recognised standardised interview schedules to collect symptom data, most retrospectively investigated early symptoms of relapse, which may involve biased or distorted recall (Fava and Kellner, 1991). Many studies had small sample sizes that also limit the generalisation of findings (median $N = 40$).

4.2. The findings

Four out of five individuals with unipolar or bipolar disorders can identify one or more early symptoms before a full relapse. In bipolar disorders, early symptoms of mania were reported by a higher percentage of individuals in comparison to early symptoms of bipolar depression (median 97% for mania vs. 82% for bipolar depression). Greater diversity has also been found to exist in the symptoms of depressive in comparison to manic prodromes (Lam and Wong, 1997; Gillin, 1998). The most robust early symptom of mania was sleep disturbance. A phenomenon also reported by Wehr et al. (1987). The most prominent early symptom of bipolar depression was mood change. However, the latter was identified by less than 50% of individuals. This review suggests that the mean duration of a manic prodrome (mean >20 days) is longer than that of bipolar depression (mean <19 days). However, comparison of the range of duration indicates greater inter-individual variation in the former (bipolar depression 2–365 days; mania 1–120 days). This raises the possibility that, unlike mania, duration of depressive prodromes is not normally distributed statistically (Francis and Gasparo, 1994).

The difference in mean duration of manic as compared to depressive prodromes may relate to different biological processes, or it may be an artefact because early symptoms of mania are readily identifiable. Scott (2001) noted that early features of mania are more distinctive as the symptoms differ qualitatively from the individuals' day-to-day experiences. Early symptoms of bipolar depression may represent a less overt quantitative shift in affect or behaviour, particularly in individuals with residual depressive symptoms (Scott et al., 2000; Fava, 1999). Such subtle changes in functioning may not be recognised as warning signals of depressive relapse until they become more severe or persistent or they are accompanied by more memorable symptoms. This would give an impression of a briefer prodrome. This notion is supported by Fava et al. (1990, 1991) who reported at least one early symptom of relapse was evident prior to the onset of depressed mood, yet mood change was the subjective experience most frequently recalled.

4.3. Implications for clinical practice and future research

Monitoring and intervening when early symptoms arise has been deemed effective in preventing or minimising the impact of relapse in affective disorders (Kupfer et al., 1989; Mander, 1990; Scott, 1995; Perry et al., 1999). The use of prompts, such as Smith and Tarrier's (1992) 40-item early symptom checklist may facilitate identification. Individuals are only likely to benefit from monitoring early symptoms if this approach is used in combination with effective coping strategies. Lam's work (Lam and Wong, 1997; Lam et al., 2001) demonstrates that effective self-management strategies for the early symptoms of mania and depression are associated with better clinical and social outcomes.

Evidence that manic prodromes are longer and easier to identify than the bipolar depressive prodromes suggests early intervention by the mental health services is more feasible for mania than for depression. Perry et al. (1999) found early symptom recognition and intervention in patients with bipolar disorders significantly reduced manic but not depressive relapses. They also noted that, once warning signals were recognised, it was easier to introduce effective pharmacological treatments for acute mania than for bipolar depression. Katon et al.'s (2001) relapse prevention program similarly reported difficulties in reducing depressive relapses (although there were other benefits). The implication of this review is that early recognition and treatment of bipolar depression is the greater challenge. This is unfortunate as evidence suggests that outcomes are also worse: clinical remission is significantly less likely to be achieved in bipolar depression than in mania (59% vs. 100%) and, even when achieved, it occurs significantly less rapidly (Hlastala et al., 1997).

Future research should involve prospective monitoring of early symptoms to provide more detailed descriptions of the duration and specific symptoms associated with prodromes of mania, bipolar depression, and unipolar depression. Investigation of prodrome duration will determine whether manic prodromes are truly longer than depressive prodromes and may determine the clinical usefulness of early symptom monitoring. Comparison of the prodromes of bipolar depression and unipolar depression may provide insights into the similarities and differences between these disorders.

Acknowledgements

Professor Scott's research on bipolar disorder is supported by a Legacy from the Searle Foundation.

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