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SPECIAL ISSUE

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Is bipolar I disorder heterogeneous?

Abstract *Objectives* The question whether bipolar I disorder should be subdivided into a preponderantly manic group (M) with no depression or only mild depression (Md) and a nuclear manic-depressive group (MD) has been rarely studied although the problem was raised more than 50 years ago. This paper seeks to elucidate this question by contributing further data. *Methods* 406 patients with mood disorders hospitalised at some time during the period 1959–1963 were followed-up every five years until 1985; mortality data were collected up to 1997. Data on episodes, outcome, suicides and attempted suicides, alcohol and substance abuse/dependence and long-term medication, as well as on personality (melancholic and manic type) were collected. Major mood disorders were subclassified according to their hospitalisation for depression (D) and/or mania (M). *Results* 30 manic patients (M/Md), 130 bipolar I (MD), 60 bipolar II patients (Dm) and 186 major depressive patients (D) were compared. The manic group differed from the bipolar I group in several variables: better school achievement, milder course of the illness (fewer recurrences), significantly less suicidality and a trend to less chronicity and more recovery. Manic patients required less long-term medication than bipolars and they differed in personality types from bipolars, the personality of manic patients being more often of the manic rather than the melancholic type, they were also more aggressive than bipolars. The family history data showed that the overall morbidity risk of first degree relatives of manic patients was significantly lower than that of bipolar patients. *Conclusions* In accord with several other studies our data point to the existence of a more manic (M/Md) group of bipolar subjects. The diagnosis predicts a better course, lower suicidality and fewer and different treatment needs than does nuclear bipolar I (MD) disorder. The M/Md groups, as clinically interesting subgroups of the mood spectrum, should become a target of further research.

Key words bipolar I disorder · mania · heterogeneity

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Introduction

Bipolar spectrum

Today we assume the existence of a wide spectrum of mood disorders (Akiskal et al. 1985) of varying severity embracing major depressive disorders (MDD = D), bipolar disorders (Dm, MD, Md) and pure mania (M) (Angst and Gamma 2002). In addition, there are subthreshold ("sub-syndromal") forms, usually sub-classified into short-term and long-term (more chronic) manifestations: minor bipolar disorders and cyclothymia, hypomania and hyperthymia (m), minor depression and dysthymia (d) (Angst et al. 2003).

This paper will mainly focus on two subgroups of the bipolar spectrum, comparing the nuclear bipolar group (MD), hospitalised for both mania and depression, with preponderantly manic bipolar patients (Md,M), who manifested only mild (Md) or no depression (M). For the purposes of comparison, data on MDD and bipolar II disorder (Dm) will also be presented.

Historical roots of monopolar mania

The concept of bipolar illness as a disease entity (*folie circulaire*) goes back to Falret (1851). Several diagnostic terms in current use were created by Kleist's school: the terms "unipolar" and "bipolar disorder" were coined by Karl Kleist (1953) and were taken over by his pupils Neele (1949) and Leonhard (1957). It is important to

note that these authors classified both pure mania and pure melancholia as "homonomic" (Kleist 1937), "unipolar" (Kleist 1953; Neele 1949) or "monopolar" disorders (Leonhard 1957). Kleist and Neele saw bipolar disorders as a combination of the two monopolar forms (pure melancholia, pure mania) with a special affinity for each other.

In other words bipolar disorder for the Kleist-Leonhard school excluded pure monopolar manic disorder. Of special interest is that Kleist and Leonhard assumed the genetic load in monopolar disorders to be much lower than in bipolar disorders, as shown by Neele's monograph (1949) and by Leonhard (1957).

Modern research on "pure" mania

Whether pure mania without severe or mild depression really exists and whether it belongs to bipolar disorder is still a matter of debate. Pure mania is certainly rare, although Kraepelin (1920) found it to be very frequent in Java; clinically most cases of mania manifest also mild (Md) or severe (major) depression (MD). Every failure to obtain full information about depression favours the diagnosis of a "pure" manic case. Retrospective diagnoses are highly suspect; long-term prospective follow-up data over several episodes (Shulman and Tohen 1994) are required in order to establish the diagnoses of pure mania with some certainty.

In the literature the term mania is often used to denote bipolar disorder (Shopsin 1979; Belmaker and Van Praag 1980); Goodwin (1990), reviewing the literature, left the question of the existence of unipolar mania explicitly open.

The question whether BP-I disorders are heterogeneous (MD vs. Md vs. M) is of great relevance for clinical, psychopharmacological and biological research and has been investigated by a number of authors.

Perris (1966) found among 156 manic-depressives 19 cases (12.2%) with monopolar mania and compared them with 138 bipolar and 139 unipolar depressives. In his family study of the first degree relatives of manics he found no depression but did find an elevated morbidity risk for bipolar disorder (7.6%), suicides (5.7%) and schizophrenia (3.3%). These figures did not markedly deviate from those of the bipolar probands: 10.2%, 4.9%, 1%.

Luka and Ciompi (1970) in a retrospective and prospective long-term follow-up study of 23 hospitalised manics found that only one case became recurrent mania, whereas 10 cases developed into Md and the others into bipolar (MD) or schizo-affective disorders.

Abrams and Taylor (1974) observed pure mania in 14 of 50 (28%) BP-I cases and found significantly less affective illness and alcoholism among first-degree relatives of M than MD.

Nurnberger et al. (1979) found that 38 of 241 (15.7%) bipolar I patients in their lithium clinic had never been hospitalised or treated for depression. They differed from the MD patients by lower rates of rapid cycling, suicide attempts and risk of illness in first-degree relatives. The family data showed there to be no BP-I secondary cases and only 2.6% BP-II disorders among the 54 relatives of unipolar manics (M). The corresponding figures for relatives of Md patients (treated for depression) were 1.8% BP-I and 5.8% BP-II, and for MD patients (hospitalised for depression) 2.9% and 4.7%. Depression and primary alcoholism were equally common among relatives of the three diagnostic patient groups (M, Md, MD).

Shulman and Tohen (1994) combined a retrospective chart review with a follow-up of 3–10 years (mean 5.6 years) and identified 6 out of 50 (12%) elderly manic episode patients as pure manics. Compared to the bipolars, the manic patients had an earlier age of onset and a longer duration of illness. The authors concluded that a firm diagnosis of unipolar mania should not be confirmed for at least 10 years and noted "the concept of unipolar mania should not be buried yet".

Palha and Arrojo (2001) found in a retrospective study of 352 bipolar women 10 cases (2.8%) of unipolar mania and stressed the existence of this diagnostic subgroup.

Yazici et al. (2002) reviewed the literature on unipolar mania and studied a clinical sample of 272 bipolar I patients. They found 16% of BP-I cases to be unipolar manics. The authors stressed the requirement of a sufficient number of episodes (three or more as suggested by Shulman and Tohen 1994) and a sufficient follow-up period (at least 4–5 years) in order to make a firm diagnosis of unipolar mania. They found pure manics to have more psychotic features than MD and to be less responsive to lithium. Interestingly enough, there was no positive family history for suicide among pure manics.

Aghanwa (2001) found pure mania (M) in 40 of 82 (47%) bipolar I patients in the Fiji islands. As originally reported by Neele (1949), the M group had a non-significant trend ($p < 0.20$) to a lower positive family history for major psychiatric disorder (9.8%) than the MD group (22.6%).

Affective personality types

Searching for heterogeneity, a few papers have included affective personality types. Leonhard (1965) diagnosed 9 of 73 (10.1%) manic-depressive patients as manifesting pure mania/euphoria, and found pure mania (Leonhard 1963) to be associated with a hypomanic temperament and hypomanic psychopathy; in addition he reported this temperament as being over-represented among the relatives.

An important methodological development was the conceptualisation of the melancholic and manic types of personality, concepts which originated in the papers of Tellenbach (1974, 1975) (melancholic type) and von Zerssen (1977) (manic type). The melancholic type is a premorbid personality structure characterised by or-

derliness, rigidity and close bonding to significant others. Von Zerssen went on to develop the biographical personality inventory (BPI) as a reliable, valid method for assessing both types (von Zerssen et al. 1998a, 1998b). The validity of the "hypomanic personality" was further supported by the development of a hypomanic personality scale (Eckblad and Chapman 1986), which proved useful as a screening instrument for bipolar spectrum disorders (Meyer and Hautzinger 2003).

Von Zerssen (2000) published a review and an integrative model for personality and axis I disorders (2002). He postulated a correlation of the premorbid personality traits of the melancholic type and the manic type with the spectrum of mood disorders. Some evidence has emerged from independent studies that the manic personality type is more common in M/Md than MD patients and the melancholic type found mostly among depressive (D) and bipolar II (Dm) patients (Zuberbühler 1994; Hecht et al. 1997, 1998).

Our typology of bipolar illness covering the subtypes (D, Dm, MD, Md, M) (Angst 1978, 1980) was based on a spectrum concept of mood disorders, and preliminary results on course, outcome and morbidity risk were published in 1980 (Angst 1980).

Our earlier analyses found a systematic increase in premorbid hypomanic personality types across this spectrum (D to Md) (Ernst et al. 1996). The present study seeks to provide further evidence of a distinction between M/Md and MD, including clinical differences in terms of course, suicide risk and personality. These two BP-I groups will also be compared to bipolar-II (Dm) and severely depressive (D) patients. Finally the morbidity risk of first degree relatives will be presented.

Methodology

The sample together with its diagnostic classification and other clinical characteristics have been fully described in recent papers on the diagnostic change from depression to bipolar disorders (Angst 2000) and the recurrence risks of mood disorders (Angst et al. 2003).

Sample and clinical assessments: The sample consists of 406 patients (186 unipolar and 220 bipolar depressive or bipolar manic) who were admitted to Zurich University Psychiatric Hospital between 1959 and 1963 with a diagnosis of mania (N = 160) or depression (N = 246) with mood-congruent or mood-incongruent psychotic features (hallucinations or delusions) including schizoaffective disorder; 61 % of the patients met criteria for psychosis at least once over their lifetime.

Psychopathology was documented by a list of 10 syndromes (Angst et al. 1968) every five years until 1985. The patients their relatives and their family doctors were contacted and their in- and outpatient records consulted. In 1985 all patients were re-interviewed and their outcome measured by the Global Assessment Schedule (Endicott et al. 1976). Data on mortality and cause of death were collected in 1991 and 1997 with the support of the Swiss Federal Statistical Office.

The course of the illness was assessed every five years (1963, 1965, 1970, 1975, 1980, 1985); we recorded beginnings and ends of episodes, syndromal diagnoses, psychotic features, treatment (outpatient, inpatient) and medication during and between episodes. Long-term medication was defined as medication administered for at least 6 months after recovery from an episode; medication (doses, plasma levels) was assessed recently in another medical dissertation by Gerber-Werder (in preparation). 197 cases received long-term medication for 6 months or more and 176 of them over 12 months or more.

The last interview took place in 1985: 42.5 % of the surviving patients could be interviewed personally; a further 22.6 % were interviewed by telephone and 3.8 % refused to be interviewed. Information on the remaining 31.1 % had to be collected from significant others. Follow-up information from interviewed relatives was obtained for 45.6 % of all patients. Reports from medical doctors were available for 30.3 % and records from psychiatric institutions for 61.2 % of the subjects. The mean follow-up period was 17.6 years (0–33 years). Mean duration of illness since the age of onset was 24.7 years (0–69). Further details on course were published by Angst and Preisig (1995).

Diagnosis: We used hospitalisation as a diagnostic criterion. All MD cases had been hospitalised for both mania and depression, whereas the M/Md cases had been hospitalised for mania only and Dm cases for depression.

The diagnosis of bipolar I vs. bipolar II disorder was made by ICD-9 criteria approximating the original criteria of Dunner et al. (1976). In a special study of a random sub-sample of 152 cases, the Research Diagnostic Criteria of Feighner et al. (1972) were applied (Grigo 1981). There was diagnostic agreement in 89 % of unipolar depression and 90 % of bipolar disorders (specificity 0.8; sensitivity 0.93). With the exception of two cases, whose hypomania lasted only one week, all bipolar II cases met the two weeks' minimum criterion for caseness. Bipolarity was assumed as soon as hypomania occurred for a few days, regardless of whether it seemed to be induced by antidepressants or not.

Education was classified into three levels: very low/low, average, above average. Personality was ascertained by Klesse and by Zuberbühler in a medical dissertation (1994), both of whom had been trained in von Zerssen's group; the raters were "blind" to the diagnoses. The instrument used was specially designed for assessing the melancholic and manic types of personality on the basis of record information (von Zerssen et al. 1994).

The "manic type", as described by von Zerssen (von Zerssen 1977), is a kind of hypomanic temperament as often found premorbidly in bipolar patients exhibiting a marked preponderance of (hypo-)manic episodes in the long-term course of their disorders (see also Kwapil 2000). In the present paper the manic type was com-

bined with another, very rare variant, the relaxed, easy-going type ("manic + relaxed"). Furthermore, three "neurotoid" types (Pössl and von Zerssen 1990) were considered: the rare nervous, tense type ("nervous"), the anxious, insecure type and its rare variant the unrealistic, dreamy type. Because of its rarity, the latter was combined with the anxious, insecure type ("anxious + unrealistic").

The construct validity of the assessment, its clinical and concurrent validity, as well as the inter-rater reliability were shown by von Zerssen et al. (1994) (see also von Zerssen 2002).

Family history: data on psychiatric disorders among first degree relatives were collected from pedigree data provided by the patients' communities of origin, from information provided by at least one relative, and from the patients themselves. Data on relatives' diagnoses were systematically collected. Diagnoses were made with ICD-9 criteria.

Statistics

Chi-square tests were used for frequency data and Kruskal-Wallis tests for continuous or rank-ordered data. The recurrence risk was computed using the multiplicative intensity model (Aalen et al. 1980), a method introduced into psychiatry by Andersen and Rasmussen (1986) and Lavori et al. (1996). The algorithm was provided by Lavori. The computations were based on follow-up in years since the first onset of the disorders. Suicides were analysed using Standardised Mortality Ratios (SMRs) and survival curves. SMRs were computed as the number of observed deaths divided by the number of expected deaths, both cumulative over age classes, and were statistically compared using t-tests. Survival analyses computed survivorship functions of suicides for the different study groups, which were statistically compared using an extension of Gehan's generalised Wilcoxon test, Peto and Peto's generalised Wilcoxon test, and the log-rank test, as implemented in STATISTICA 6.0. The morbidity risks among first-degree relatives were computed according to the methods proposed by Weinberg (1920) (applied here to unipolar cases) and by Slater (1938) (applied to bipolar cases) respectively. These methods adjust the total number of relatives (the denominator in the equation of morbidity risk) by weighting relatives in inverse proportion to the morbidity risk of their age group. Thus, relatives who have not yet reached the risk period of the disorder are discounted (i. e. assigned weight 0), those within the risk period are counted according to their morbidity risk (i. e. assigned a weight between 0 and 1, increasing with age), and those beyond the risk period are counted fully (weight 1). The Weinberg method is approximative, in that it weights at 0.5 all relatives within the risk period. The method of Slater (1938) is more exact, in that it derives age-specific weights from the morbidity risks of an actual bipolar population. We used the simpler Weinberg method for unipolar patients, because no age-specific weights for unipolar populations were available. Analyses were performed with SAS 8.2 and STATISTICA 6.0.

Results

We computed comparatively all four groups of mood disorders, 186 cases with major depressive disorders (MDD), 60 with bipolar II (BP-II) disorders, 130 with MD (BP-I) and 30 with M/Md (pure or preponderantly manic cases). The 30 subjects with M/Md consist of 16 Md patients (hospitalised for mania with a lifetime history of mild depressive episodes), and 14 pure manics (M), who never reported any depressive episodes. The latter two groups will be merged for the analysis in order to have sufficient cell occupancies.

All results will be presented for the four groups with a special focus on M/Md vs. MD patients in order to check the question of heterogeneity of bipolar I disorders.

Table 1 shows group differences in terms of demographic variables, course and outcome, suicides, substance abuse/dependence, long-term medication and family history.

Sex

A preponderance of women was found mainly in MDD (77.4 %) and Dm (86.7 %), whereas in MD it was mild (61.5 %) and in Md non-existent (50 %); MD and Md did not differ statistically to any significant degree (small N's).

Psychotic symptoms

MD and Md cases were more severely affected by psychotic symptoms and mood-incongruent features: psychotic symptoms (delusions, hallucinations) were found in about 80 % of MD and Md cases and in about 50 % of D and Dm cases; mood-incongruent features were present in about 79 % of MD and Md cases and in only about 30 % of D and Dm patients.

During their illness many patients experienced psychotic episodes (catatonia, delusions, hallucinations) without a simultaneous depressive or manic syndrome. They can be considered as affect-dominant schizo-affectives. Such psychotic episodes occurred in about 10 % of D and Dm cases and in about one third of MD and Md cases.

Onset, recurrence, chronicity and recovery

The two BP-I groups (MD, M/Md) did not differ in age of onset, but their age of onset was definitely much earlier than that of D and Dm patients.

Table 1 Characteristics of subgroups

	D (MDD) (1)	Dm (BP-II) (2)	MD (BP-I) (3)	Md (BP-I) (4)	p 1–4	p 3–4
Subjects (N)	186	60	130	30		
Female (N)	144	52	80	15	0.0001	0.83
(%)	77.4	86.7	61.5	50.0		
Age at follow-up (1985) (mean)	66.6	70.2	64.1	60.5	0.0001	0.14
School achievement						
• low	7.5	15.0	19.4	3.3		
• medium	88.2	80.0	69.0	90.0	0.0016	0.053
• high	4.3	5.0	11.6	6.7		
Illness						
Psychotic features						
• none	49.5	56.7	21.5	20.0		
• mood-congruent	18.8	13.3	10.0	6.7	0.0001	0.82
• mood-incongruent	31.7	30.0	68.5	73.3		
Psychotic episodes without mania or depression	9.7	10.0	37.7	33.3	0.0001	0.90
Age of onset (episode) (mean)	44.0	37.9	30.0	31.0	0.0001	0.25
Number of episodes (median)	4	10.5	11	7	0.0001	0.0006
N of man. episodes (mean)	0	3.2	8.0	7.3	0.0001	0.98
N of dep. episodes (mean)	5.3	13.8	8.4	2.1	0.0001	0.0001
Number of episodes/year (median)	0.21	0.33	0.38	0.32	0.0001	0.03
Number of episodes/year (mean)	0.29	0.42	0.27	0.24	0.0001	0.06
• N of man. episodes/year (mean)	0.00	0.12	0.25	0.28	0.0001	0.36
• N of dep. episodes/year (mean)	0.28	0.46	0.27	0.07	0.0001	0.00
Course and outcome					0.0679	0.23
• recovered (5 + years)	35.0	25.0	20.8	33.3		
• recurrent	39.8	53.3	53.9	56.7	0.001	0.15
• chronic	11.8	15.0	15.4	6.7		
• suicide	13.4	6.7	10.0	3.3	0.23	0.25
Standardised mortality ratios for suicides	25.7*	11.3	14.2*	5.2		
% suicide attempts	21.4	26.7	29.2	10.0	0.08	0.03
N of suicide attempts (mean)	0.37	0.60	0.72	0.17	0.25	0.10
Outcome last interval (GAS)						
• 91–100 (%)	13.0	10.0	5.4	13.3		
• 61–90 (%)	47.8	51.7	32.6	26.7	0.0041	0.47
• 31–60 (%)	28.8	28.3	50.4	50.0		
• 1–30 (%)	10.3	10.0	11.6	10.0		
Substance abuse/dependence						
• alcohol	5.4	3.3	14.6	10.0	0.0125	0.51
• other substances	4.3	8.3	2.3	0	0.1532	0.41
Morbidity risk of first-degree relatives (%)						
• Depression	11.9	10.2	8.3	6.0	< 0.05	0.79
• Depression + SAD	12.5	11.1	11.2	6.0	0.06	0.21
• BP spectrum	1.4	3.6	3.5	4.0	< 0.05	0.36
• BP spectrum + SAM	1.9	4.5	6.4	4.7	< 0.05	0.26
• Schizo-affective psychosis[1]	1.9	3.3	7.0	2.7	< 0.05	0.04
• Schizophrenia	1.1	1.5	2.0	0.7	NS	0.26
• Total	16.3	18.6	20.8	13.4	0.06	0.05
Long-term medication (6 + mths)						
• Lithium	4.3	23.3	42.3	23.3	0.0001	0.06
• Clozapine	3.8	1.7	19.2	6.7	0.0001	0.10
• Neuroleptics	25.8	26.7	58.5	33.3	0.0001	0.01
• Antidepressants	31.7	46.7	33.9	6.7	0.0021	0.003
• Benzodiazepines	8.6	23.3	16.9	6.7	0.0096	0.16
• Hypnotics	4.3	10.0	13.1	0.0	0.0100	0.04
• no long-term medication	63.4	46.7	33.1	66.7	0.0001	0.0007

* sign. $p < 0.05$ compared to the Swiss population
SAD schizo-affective depressives; *SAM* schizo-affective manics
[1] Schizo-affective psychosis unspecified

The total number of episodes differed greatly across the diagnostic groups, being lowest in the depressed and more manic groups. Major depressives had the lowest episode frequency, followed by the manic group (M/Md). The M/Md group had significantly fewer episodes than the MD group, but exclusively because they had fewer depressive episodes; they also had fewer depressive episodes per year of follow-up.

Chronicity (defined as no recovery from the last episode after a minimum of 2 years) was slightly lower in the Md group (6.7 %) compared to MD cases (15.4 %, $p < 0.18$). Compatible with this finding, recovery (defined as no episodes during the last five years and a GAS score of 61 or more) was found in 33.3 % of Md and only in 20.8 % of MD cases ($p < 0.15$). On the other hand, all four groups of mood disorders showed a poor outcome, defined by a GAS score of 1–30 in about 10 % of cases.

Recurrence

A similar trend is visible in episode recurrence. The cumulative intensity curves demonstrate a much lower recurrence risk, measured as transitions from healthy to ill, among Md and D compared to Dm and MD cases (Fig. 1). The latter two groups did not differ from each other, having about double the recurrence risk of the Md and D groups, a finding compatible with the total number of episodes observed. The better course of Md cases was also clear when we computed the % of their lives spent in episodes since the onset of the disorder. It was significantly ($p < 0.002$) lower among Md cases (13 %) compared to the other three groups (19–21 %).

Limitations

The analyses on course and outcome suffer from the small cell occupancy in the Md group (N = 30) if broken down into subgroups. Bearing this in mind we cannot exclude a trend to a better course and outcome of Md compared to MD cases

Suicides

These were lowest in the Md group (3.3 %) and three- to four-fold higher among MD (10 %) and D (13.4 %) patients. This finding is confirmed by standardised mortality ratios (SMRs): Md = 5.2, MD = 14.2 and D = 25.7. The facts are best illustrated by the survival curves (Fig. 2).

Long-term medication

Patients receiving further maintenance medication for six months or more after remission were considered to have been treated long-term. There are considerable differences in the treatment given to the four diagnostic subgroups: Depressive patients were rarely treated with lithium or clozapine, but one fourth received neuroleptics (against psychotic symptoms, agitation and insomnia). On the other hand antidepressants, benzodiazepines and hypnotics were rarely given to the manic group (0.0–6.7 %). Compared to bipolar I patients, manic patients were also much less frequently medicated with lithium and clozapine. On the whole, manic patients received significantly less long-term medication than the three other mood disorder subgroups.

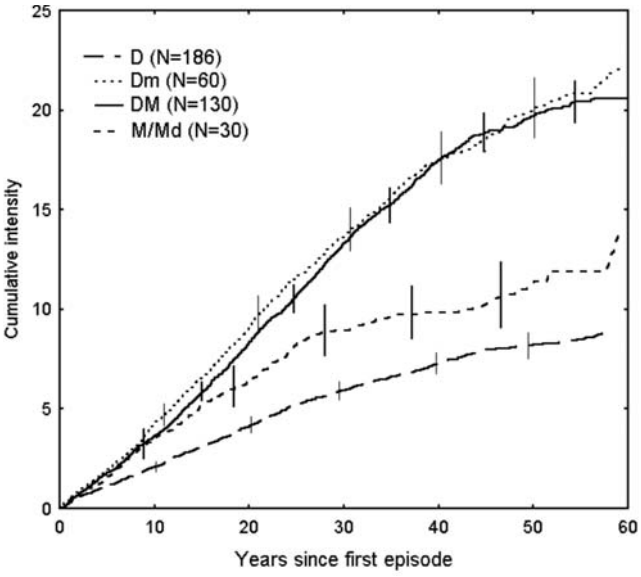

Fig. 1 Recurrence risk of different subtypes of mood disorder (means and 95 % confidence intervals)

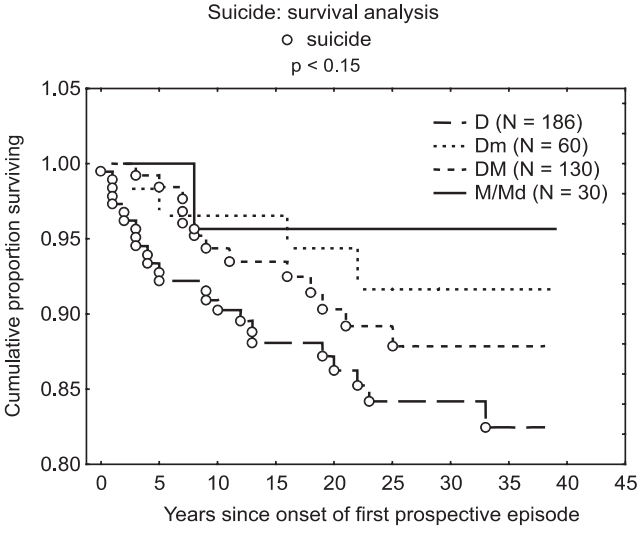

Fig. 2 Survivorship function of suicides for different subtypes of mood disorder

Family history

The morbidity risk for the depressive spectrum among first degree relatives was highest in the purely depressed group (D) with 11.9%, it was very similar (10.2%) among bipolar II patients (Dm), slightly lower among MD patients (8.3%) and lowest among relatives of manics (6%). A contrary trend was found for bipolar spectrum disorders among relatives; these were more prevalent in the families of manics (4%) and less so in families of MDD patients (1.4%), whereas the remaining two groups (Dm, MD) stood somewhere in between. The overall morbidity risk for affective, schizo-affective and schizophrenic disorders among relatives was significantly lower in the manic (13.4%) than in the bipolar group (20.8%).

Personality

Table 2 shows systematic, significant differences in the distribution of manic versus melancholic types of personality: the major depressive group was characterised by high rates of melancholic and low rates of manic personality types; the reverse was true of manic patients (Md), amongst whom relatively high rates of manic personality and lower rates of melancholic personality types were found. The other two groups (Dm, MD) took intermediate positions, compatible with the hypothesis that melancholic personalities are correlated with the depressive and the manic personalities with the manic component of mood disorders.

An interesting and counter-intuitive finding was that an anxious-insecure type of personality was two to three-fold more common among M/Md and MD patients than among D and Dm patients. Manic patients differed significantly from the core group of BP-I patients, in their greater aggression and their manic type of personality.

Discussion

Most current research on bipolar disorder is limited to bipolar I (BP-I) disorders: the majority of acute and maintenance treatment studies, for instance, have selected BP-I patients during a manic episode, making no distinction between M, Md and MD. Our study set out to compare a prototype bipolar case MD (suffering from both hospitalised mania and hospitalised depression) with Dm (suffering from hospitalised depression) and M/Md (suffering from hospitalised mania). The use of hospitalisation as a diagnostic classifier was originally suggested by Dunner et al. (1976). Hospitalisation reflects severity, which was confirmed by the high rates of psychotic features found in our sample, especially among MD (78.5%) and Md (80%) patients, although we did not find a higher rate of psychotic features among Md patients as reported by Yazici et al. (2002).

Studies on Md/M are difficult to carry out, because there are few manic patients who suffer from mild depression (Md) or no depression (M) at all. In our study, 18.7% of our 160 BP-I cases were Md/M cases, a rate which is roughly comparable to that of Perris (1966) who reported 12.2%, Shulman and Tohen (1994) (12%) and Nurnberger et al. (1979) (15.7%), but lower than those of other investigators, like Abrams and Taylor (Abrams and Taylor 1974) who found 28% and Aghanwa (2001) who reported the unusual rate of 47%. Our study, like others, suffers from the small number (N = 30) of Md/M subjects; therefore negative findings may not always be conclusive (type II errors) and we are also interested in observing certain trends in order to create new hypotheses.

The hypotheses tested in this paper derive from the literature summarised in the introduction (Neele 1949; Kleist 1953; Leonhard 1957; Perris 1966; Abrams and Taylor 1974; Nurnberger (Jr) et al. 1979; Shulman and Tohen 1994; Yazici et al. 2002) and our own earlier investigations (Ernst et al. 1996). We assumed that Md/M patients, who by definition suffer little from depression, would be less suicidal than MD, Dm and D patients. Building on Kleist's concept, we hypothesised that the

Table 2 Personality characteristics

Personality types	D (MDD) (1)	Dm (BP-II) (2)	MD (BP-I) (3)	M/Md (BP-I) (4)	p 1–4	p 3–4
Subjects	182	59	125	30		
Abnormal personality (1–7)	3.1	3.5	4.0	4.5	0.0000	0.209
Personality types	%	%	%	%		
• nervous tense	2.8	–	9.6	3.3	0.009	0.46
• anxious + unrealistic	4.4	3.4	10.4	10.0	0.0001	0.16
• melancholic	86.8	76.3	50.4	36.7	0.0001	0.06
• manic + relaxed	6.0	20.3	29.6	50.0	0.0001	0.03
Aggressive						
• low	39.6	32.2	16.0	10.0		
• moderate	57.7	59.3	62.4	43.3	0.0001	0.020
• high	2.8	8.5	21.6	46.7		

course of M/Md cases (as unipolar disorders) would be similar to that of unipolar depression and that the morbidity risk among their relatives would be lower, although Perris' (1966) findings were negative in this respect. Md and depressed patients should consequently show lower recurrence rates, fewer episodes and a better outcome than MD patients. On the basis of von Zerssen's concept we also hypothesised that the manic personality type would be more common among manic patients. Our data partly bear out these hypotheses.

The suicide rate among our manic patients (Md/M) was relatively low: it was one third that of MD patients and one fourth that of major depressive patients, a finding confirmed by the more sensitive Standardised Mortality Ratios. In addition, the suicide attempt rates were half or one third those found in the other three groups. These results converge with Nurnberger et al's (1979) finding that suicide attempt rates were lower among relatives of manic than of BP patients.

Unlike Shulman and Tohen (1994) in their study of elderly bipolars, we could not find any difference in age of onset between manics and bipolars. We did find a clearly more benign course of the illness in manic versus true bipolar patients: manics experienced significantly fewer episodes over their lifetime, which is also illustrated by the recurrence risk curves of transitions from healthy to ill. The lower episode frequency is ascribable to the small number of depressive episodes, whereas manic episodes were equally present in manic and MD patients. An interesting result of our study was the trend (small N's, $p < 0.15$) to lower rates of chronic outcomes and higher rates of recovery (over at least five years) among manics versus bipolars. Pfohl et al's (1981) refutation of the existence of pure mania on mathematical grounds assumed that manic patients had at least as many recurrences as MD patients; this assumption is disproved by our data.

The better school achievements of the manic group ($p = 0.053$) is a finding of some interest. It comes as no surprise that both the bipolar and the manic groups were at much greater risk than depressive or bipolar-II patients of developing alcohol abuse/dependence. This finding confirms that of Nurnberger et al. (1979) and is also fully compatible with the results of the Zurich cohort study of a community sample (Angst et al. in preparation), which demonstrated that an increased risk of developing alcoholism correlates less with depression than with hypomania/mania.

Of no surprise either were the findings regarding affective personality types: a manic type of personality tended to be more and a melancholic type less frequent among manics than bipolars ($p < 0.06$). The systematic decrease in melancholic and anxious personality types across the spectrum D-Dm-MD-Md/M was an interesting finding. Equally interesting was the systematic increase in the manic type and aggression across the spectrum. These results confirm von Zerssen's (2002) model and earlier reports comparing depressives with bipolars (Hecht et al. 1997).

The genetic data are compatible with the assumption of a genetic vulnerability due to multiple genes. The phenotype of the probands corresponds to some extent to the relative proportion of manic and depressive first degree relatives: manics have more manic relatives, depressives more depressive relatives; but depressive and manic/bipolar relatives occur in all subtypes. Across the spectrum D-Dm-MD-Md/M the morbidity risk for depression decreased steadily from D (11.9%) to M/Md (6%), whereas there was a steady increase in the morbidity risk for the bipolar spectrum from 1.4% to 4%. The four proband groups thus form a continuum of subgroups within the spectrum from a genetic point of view also. The findings of Nurnberger et al. (1979), those of Neele (1949) together with our own presented here would certainly warrant a specific molecular-genetic investigation of manics versus bipolars.

One question to which our study could not contribute any data was the response to long-term medication. An important issue is the possibility that manics respond less well than bipolars to lithium, as found by Yazici et al. (2002). Recent reports suggest that olanzapine is preferable for patients with a predominance of manic episodes (Grof 2003). Of some interest was our finding that the manic group required much less long-term medication than the other subgroups of mood disorders, which fits the results indicating that M/Md has a more benign course

Conclusion

Although the diagnostic manuals distinguish between depression, bipolar II and bipolar I disorders there is evidence for a spectrum concept of mood disorders, which considers the subgroups as the result of different constellations of multiple genes for depression and for mania. The group of mania with mild depression and the group with pure mania would be further subgroups of this spectrum.

Our results provide strong evidence for keeping manic patients as a separate diagnostic subgroup from classic bipolars, which then would become more homogeneous. The Md/M subgroups may differ in course and treatment response from classical bipolars (MD). It would therefore be highly recommendable for "pure" manics to be identified in drug trials, which recruit manic patients, in order to check the question of different treatment responses; this would be equally important for acute and maintenance studies.

Limitations

The converging studies on which the conclusions are based, including our own, involve relatively small samples of manics, because they are much less prevalent than classic bipolar I patients. Our sample of M/Md ($N = 30$) was too small to be broken down into M and

Md. Although the results support the hypothesis of the heterogeneity of bipolar I, they cannot give definitive proof; they need to be replicated. In addition, our findings are limited to a sample of severe hospitalised patients. Our diagnostic classification was much closer to the criteria of Dunner et al. (1983) than to DSM-IV (American Psychiatric Association 1994) or ICD-10 (World Health Organisation 1992).

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