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Single Episode of Major Depressive Disorder

First Episode of Recurrent Mood Disorder or Distinct Subtype of Late-onset Depression?

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Summary. Of 687 consecutive inpatients and outpatients with primary major depressive illness, 213 (31%) were categorized as single episode (SE) by DSM-III-R criteria. Systematic evaluation of familial, sociodemographic, temperamental and symptomatological characteristics permitted the nearly equal division of SE into two categories: a. early-onset (< 45 years) "first episode" superimposed on either depressive or hyperthymic temperaments (against a bipolar and unipolar familial background), more severe depression, higher rates of suicide attempts, greater anxiety-somatization and psychotic tendencies, and with the potential for recurrence; b. late-onset (≥ 45 years) isolated episode (against an unipolar familial background) with greater life stressors, pursuing a protracted course with less likelihood of recurrence. In most other respects, early-onset SE was intermediate between recurrent major depression and late-onset SE. The implications of these findings for the now largely abandoned category of "involutional melancholia" are discussed.

Key words: Late-onset depression – Single-episode depression – Hyperthymic and depressive temperaments

Introduction

A first major depressive episode (MDE) that does not recur during follow-up has been reported to be relatively uncommon (Kinkelin 1954; Stenstedt 1959, Astrup et al. 1959, Angst 1978; Akiskal et al. 1978, Zis et al. 1980). Thus, at the first episode, the clinician is expected to assess which disorder (recurrent unipolar or bipolar) the depressive episode will ultimately belong to. However, a substantial minority, as many as one out of three depressives (Kinkelin 1954, Perris 1968) do not progress beyond an isolated single episode (SE). According to Akiskal and McKinney (1973), these isolated depressive episodes could be determined by the action of multiple environmental factors superimposed on a predisposing ground, rather than strong genetic factors which appear important for bipolar and recurrent depressive disorders. Thus, losses, physical illnesses, and deficient social support might have a formative influence in the origin of an isolated single episode of depression in the absence of a past or family history of mood disorders. This conceptualization was in part upheld in a previous paper by our group (Musetti et al. 1989) on late-onset depression that appeared triggered by stressors in the relative absence of familial-genetic factors.

The differentiation between "single" and "first" depressive episode could be obtained by the exclusion of those indicators of recurrence such as loaded pedigrees, bipolar family history, early onset, post-partum and psychotic episodes, and pharmacologic hypomania (Winokur 1974, Akiskal et al. 1979, 1983, Strober and Carlson 1982, Winokur et al. 1982), and pre-existing dysthymia (Keller et al. 1983, Klein et al. 1988).

In a previous study of 405 patients with MDE (Cassano et al. 1989), those with a single major depressive index episode in the absence of a history of depressive, hypomanic, manic or mixed episodes were recognized as having distinct features characterized by a more frequent chronic course, a greater incidence of stressors preceding the episode, and an older age at onset than that of bipolar and recurrent depressions. However, as in the Pichot et al. study (1979), no clear-cut symptomatological differences emerged between younger and older depressives, even after controlling for the pathoplastic effect of aging. Neither our study, nor previous studies reviewed in Pichot and Pull (1981) have resolved the nosologic status of single-episode depressions, especially those with late-onset. For this reason, we decided to further investigate the characteristics of SE major depression among a larger population of 687 depressive patients, specifically aiming at the identification of a subgroup of depressives with a stable diagnosis of SE distinguishable from those with the potential for recurrence

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subsequent to index diagnosis. The attempt then was to characterize patients with SE on the basis of age at onset, affective temperaments, family history, stressors, chronicity, melancholic features, and psychotic symptoms. Subgroups of SE depressives were compared with recurrent unipolars to identify potential predictors of course and evolution. Therefore, the study attempts to shed light on the following main points:

1. the historical debate initiated by Kraepelin (1896) in the fifth edition of the Lehrbuch (only sixth edition exists in English 1990) on the existence of "involutional melancholia" or late-onset depression as a distinct entity:

2. clinical characterization of late-onset isolated SE as far as symptomatology, course and tendency to chronicity is concerned;

3. the role played by stressors, family history and temperamental dysregulation in the SE variety of depressive illness:

4. identifying SE in which subsequent recurrent unipolar to bipolar course is likely to occur.

Patients and Methods

The total study population comprised 687 major depressives – of whom 211 (30.7%) were male and 476 (69.3%) female – consecutively admitted to the University of Pisa Psychiatric Institute and affiliated clinical facilities. Their mean age at index evaluation was 50.26 years (SD 14.3) with a range of 18–82 years. To focus on as homogeneous as possible primary mood disorders, the following categories were excluded: patients whose depression was an understandable development in the setting of an organic mental disorder, mental ratardation or a neurologic disorder: a psychoactive substance use disorder that dominanted the clinical course: depression concomitant with mental retardation, schizophrenia, panic, phobic, obsessive-compulsive and somatoform disorders, and anorexia-bulimia.

Diagnostic subtyping of subjects was accomplished with the Semistructured Interview for Depression (SID) (Cassano et al. 1987), which represents a collaborative effort between the Institute of Clinical Psychiatry of the University of Pisa, Italy, and the Section of Affective Disorder at the University of Tennessee, Memphis, USA (more recently transferred to the University of California at San Diego, USA). It is modified from the mood clinic semistructured interview (Akiskal et al. 1978), used extensively in University of Tennessee Clinical Research. The SID itself is designed to diagnose MDE (American Psychiatric Association 1987) and to collect systematic anamnestic data on number and duration of previous episodes, number of suicide attempts, temperamental aspects, interepisodic residual phenomena, response to previous treatment, "stressors" related to the onset of the index episode, and the presence of melancholia (or endogenous clinical features), as well as congruent and incongruent psychotic features. Family history data are collected by Winokur's approach as incorporated into the family history method of the Research Diagnostic Criteria (Andreasen et al. 1977).

The major innovation in this instrument is the provision of operational criteria for depressive and hyperthymic temperaments representing the University of Tennessee modification (Akiskal and Mallya 1987) of the Schneiderian descriptions (Schneider 1959). The depressive temperament requires the presence of at least five of the following items: 1. gloomy, pessimistic, humourless or incapable of fun: 2. quiet, passive or indecisive; 3. skeptical, hypercritical or complaining: 4. brooding and given to worry: 5. conscientious or self-disciplining: 6. self-critical, self-reproaching, or self-derogatory: 7. preoccupied with inadequacy, failure and negative events to the point of feeling morbid enjoyment at one's own failures. As for the hyperthymic temperament, again at least five of the following items are required: 1. irritable, cheerful, overoptimistic or exuberant: 2. naive, overconfident, self-assured, boastful, bombastic or grandiose: 3. full of plans, improvident, carried away by restless impulses; 4. overtalkative; 5. warm, people-seeking or extroverted: 6. overinvolved and meddlesome; 7. uninhibited, stimulus-seeking or promiscuous. Inquiry on temperaments is made about the habitual self of the patient form both patient and significant others. In our experience, reporting on clinical, age and gender correlates of smaller clinical subpopulations in this series (Cassano et al. 1989, Musetti et a. 1989, Perugi et al. 1990), both hyperthymic and depressive temperaments reflect easy-to-detect characteristics which are recognizable in index episodes and are not state-dependent, thereby supporting the utility of the present instrument in defining MDE subcategories on the basis of temperamental profiles. Klein's (1990) experience with the depressive temperament also indicates lack of state dependency and longitudinal stability.

The SID permitted us to identify the following subtypes of primary MDE modified from the classificatory schema of Akiskal (1983a, b): 1. single-episode major depression; 2. recurrent unipolar major depression: 3. bipolar I (BI) disorder, MDE with a history of full-blown manic symptomatology: 4. bipolar II disorder (BII), defined as MDE preceded or followed by hypomania: 5. MDE with pre-existing hyperthymic temperament (Akiskal and Akiskal 1988) – but in the absence of hypomania or mania – refers to apparently "unipolar" depressives with hyperthymic temperament (U-HT). In view of their small number, in previous publications (Cassano et al. 1988, 1989, Musetti et al. 1989, Perugi et al. 1990), we had tentatively combined groups 4 and 5 into the larger BII category. Given the much larger size of the present study population – and in accordance with current clinical convention in the present communication, MDE with hyperthymic temperament will be considered with unipolars, recurrent or single episode (U-HT).

The SID instrument partly derives from other operationalized procedures with published reliabilities (Andreasen et al. 1977, American Psychiatric Association 1987), as well as new procedures introduced by us to address the temperamental foundations of affective illness and the assignment of patients to the proposed bipolar and depressive subtypes. Intercentre (i.e. Pisa-Memphis) reliability has been documented elsewhere (Cassano et al. 1992). We have now systemically used this instrument for over 5 years, conducting at least 1000 interviews, and psychiatrist participating in this series of studies have extensive and systematic training in the diagnostic approach, which has proved reliable. The semistructured face-to-face interview, which lasts 30–60 min, is well accepted by patients (Cassano et al. 1987). Information obtained from patients is routinely supplemented or corroborated by that obtained from significant others who accompany the patient to our clinic; this is of particular significance for familial psychopathology, and temperamental measures which are based on patients' habitual functioning prior to affective episodes. All clinical information is gathered by psychiatrist with at least 7 years of post-doctoral clinical experience; all clinical data are ultimately presented of the senior Italian psychiatrist on our team (G.B.C.) who, during a briefer face-to-face interview, provides the final consensus diagnostic subtyping.

The SID approach to the diagnosis of manic and hypomanic episodes is documented in previous papers (Akiskal et al. 1989, Cassano et al. 1989). The specific criteria, derived from Akiskal et al. (1977), which distinguish mania from hypomania require one or more of the follwing: 1. meaningful conversation is difficult to maintain for any length of time; 2. euphoric or ecstatic mood deteriorates to querulous belligerence; 3. affective hallucinations of frank delusions of grandiose ability or identity, delusions of assistance or persecution, delusions of reference, and delusions of love; 4. loss of insight and judgment to such a degree that frenzied

expansive activity leads to marked social impairment. The SID criteria for the diagnosis of hypomanic episodes, also adopted from Akiskal et al. (1977) as well as Akiskal and Mallya (1987), are those for DSM-III mania but at a lower symptomatologic threshold, meeting all three of the following qualifications: 1. absence of psychotic manifestations (as already summarized for mania); 2. mood is predominantly elated, no more than occasional irritability; 3. duration as short as 2 days suffices if the typical symptomatologic picture develops. Both spontaneous episodes and those occurring in the course of antidepressant of ECT treatment were counted as long as they satisfied the symptomatologic criteria; these are based on prospective observations by Akiskal et al. (1983). Finally, pre-existing cyclothymia was considered sufficient to qualify for hypomanic episodes because, by definition, it consists of repeated episodes of hypomania alternating with mini-depressions. The reliability of all of these procedures has recently been documented (Cassano et al. 1992).

For the assessment of symtomatology, in the present report, we relied primarily on the Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960, 1967) which, in our centre is completed by psychiatrists.

Statistical methods included ANOVA followed by Scheffé comparisons of pairs of means for continuous or dimensional variables, and Chi-Square for the categorical data. We conservatively used two-tailed statistics.

Results

Among our study population of 687 patients selected on the basis of an index MDE, 213 (31.0%) did not show previous depressive, or manic and hypomanic episodes and were classified as "single-episode" depressives by DSM-III-R criteria. The general characteristics of SE depression are shown in Table 1.

In the results to be presented, we comment on selected variables which are most relevant to the issues surrounding the subtyping of SE major depressions.

The mean age of SE Patients was 49.6 years with mean age at onset of 48.0 years

We subdivided SE into subgroups over ($n = 130$) and below ($n = 83$) 45 years of age at onset. The early-onset subgroup showed a nonsignificantly higher percentage of males (43.5% vs 31.5%) and a percentage of hyperthymic temperament essentially equal to that of the older-onset subgroup (10.8% vs 11.5%). By contrast, the depressive temperament was significantly more prevalent in the early onset subgroup (49.4% vs 30.0%, $P < 0.01$). The latter finding can also be observed in Fig. 1 which graphically illustrates SE depressives with and without depressive temperament by age at onset.

Stressors were nonsignificantly more frequent in the late-onset subgroup (61.4% vs 71.5%). Suicide attempts differed significantly, with a higher frequency among the early-onset SE depressives (10.8% vs 2.3%; $P < 0.05$). Other symptomatological features and family history (for unipolar and for bipolar disorder) did not differ in the two subgroups.

Comparing these two age-at-onset subgroups of SE depressives with recurrent unipolars (Table 2), the early-onset SE showed a lower percentage of chronic course than the late-onset, lower incidence of stressors, higher percentage of depressive temperament and more frequent suicide attempts (all significant at $P < 0.01$). No differences in hyperthymic temperament, nor in terms of family history emerged. In all of these respects, the early-onset SE tended to occupy either an intermediate position between late-onset SE and recurrent unipolar, or a position closer to recurrent.

Table 1. General profile of 213 SE depressives

% Male	36.2	
$\bar{x}$ Age (SD)	49.6	(15.5)
$\bar{x}$ Age at onset (SD)	48.0	(15.3)
$\bar{x}$ Length of illness in years (SD)	1.6	(2.5)
$\bar{x}$ Age 1st hospitalized (SD)[a]	46.1	(15.4)
$\bar{x}$ N Hospitalizations (SD)[a]	0.2	(0.6)
% Chronic course (>24 months)	26.8	
% Depressive temperament	37.6	
% Hyperthymic temperament	11.3	
% "Stressors"	67.6	
% Suicide attempts	5.6	
% Melancholia	47.4	
% Psychotic features:	5.2[b]	
Mood-congruent	5.2	
Mood-incongruent	0.9	
Total HAM-D	20.75	
First-degree family history (%)		
Major depression	31.5	
Bipolar disorder	3.8	
Alcohol abuse	6.6	
Schizophrenia	0.9	

[a] $n = 42$

[b] The total does not exceed 5.2%, because some patients had both congruent and incongruent delusions

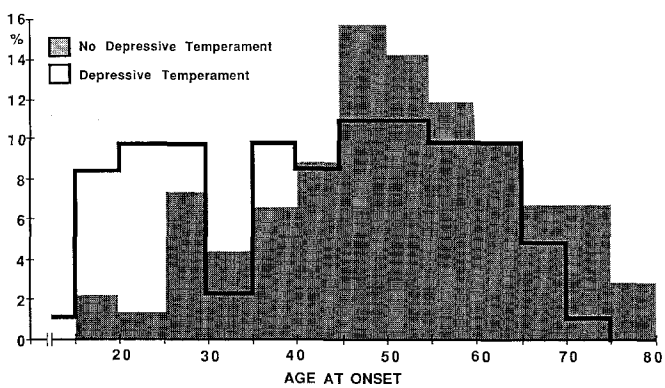

Fig. 1. Age at onset of single-episode major depression with and without depressive temperament

Among SE Patients, 77 (36.2%) were Male and 136 (63.8%) Female, with a Female/Male ratio of 1.8:1

The comparative analysis by gender showed males to have a younger, though not statistically significant, age at onset (45.9 vs 49.1 years), a significantly earlier age at first hospital admission (40.2 vs 52.6 years, $P < 0.01$), a significantly higher number of hospitalizations (0.4 vs

Table 2. Demographic and clinical features of early- and late-onset SE versus recurrent unipolars

	Recurrent ($n = 342$)	<45 yrs SE ($n = 83$)	≥45 yrs SE ($n = 130$)	
Age ($\bar{x}$)	51.9	33.3	59.1	[a]
Age at onset ($\bar{x}$)	36.7	31.3	57.6	[a]
Chronic course (%)	15.2	24.4	28.1	<0.01
Stressors (%)	49.4	60.3	71.9	<0.001
Suicide attempts (%)	13.7	11.5	2.2	<0.01
Depressive temperament (%)	43.9	50.0	30.4	<0.01
Hyperthymic temperament (%)	12.9	11.5	11.1	ns

[a] Not compared, because any differences would largely be definitional

Table 3. Demographic and clinical features in SE depressives subdivided into three subgroups according to temperament

	Hyperthymic ($n = 24$)	Depressive ($n = 80$)	Neither ($n = 109$)	
% Male	66.7	32.5	32.1	<0.01
Age (years)	51.6	45.1	52.6	<0.01
Age at onset (years)	49.6	43.1	51.2	<0.01
Suicide attempts	4.2	10.0	2.8	ns
Total HAM-D	22.5	21.8	19.6	<0.01

0.2, $P < 0.05$), and significantly more frequent hyperthymic temperament (20.8% vs 5.9%, $P < 0.01$); the depressive temperament was nonsignificantly higher among women.

The Mean Length of Illness was 1.6 Years, and a Chronic course – Strictly Defined as a duration of the Index Episode Longer than 2 Years – was Present in 57 (26.8%) of SE Patients

The comparison between SE patients with duration of illness under and over 24 months showed no differences, except for a greater mean number of hospitalizations in those with chronic course (0.5 vs 0.2, $P < 0.01$). We subsequently compared SE with a length of illness under and over the mean duration (1.6 years) of the SE population. Those patients with longer duration of the episode (≥ 1.6 years) were of older age at first hospitalization (49.0 years vs 42.3 years, $P < 0.01$), and had experienced a greater number of hospitalizations (0.4 vs 0.1, $P < 0.01$). Hyperthymic temperament was about equally prevalent in those with shorter and longer duration of episode (11.5% vs 10.8%), and depressive temperament was somewhat more prevalent among those with longer duration (44.6% vs 33.8%).

Of the Patients, 144 (67.6%) had Experienced Stressors Preceding the Index Episode

Patients reporting a stressor chronologically related to the index episode differed significantly from those not reporting in terms of the following characteristics: older age (51.5 years vs 45.8 years, $P < 0.05$), later age at onset (49.7 years vs 44.2 years, $P < 0.05$), and age at first hospitalization (50.1 years vs 38.9 years, $P < 0.05$). The

Table 4. Demographic and clinical features in SE depressives with and without affective temperaments

	SE with temperament ($n = 104$)	SE without temperament ($n = 109$)	P
% Male	40.4	32.1	ns
$\bar{x}$ Age	46.6	52.6	<0.01
$\bar{x}$ Age at onset	44.6	51.2	<0.01
$\bar{x}$ Length of illness	2.0	1.4	ns
$\bar{x}$ Age 1st hospitalized	45.7	46.4	ns
$\bar{x}$ No hospitalizations	0.2	0.2	ns
% Chronic course (>24 months)	26.0	27.5	ns
% "Stressors"	67.3	67.9	ns
% Suicide attempts	8.7	2.8	ns
Family history			
Major depression	31.7	31.2	ns
Bipolar disorder	7.7	0.0	<0.01
Alcohol abuse	7.7	5.5	ns
Schizophrenia	1.0	0.9	ns

percentage of hyperthymic temperament was nonsignificantly higher in those having had a stressor preceding the index episode (13.2% vs 7.2%), whereas the depressive temperament was nonsignificantly higher in subjects *without* stressors (42.0% vs 35.4%).

A Depressive Temperament was Recorded in 80 Patients (37.6%) and Hyperthymic in 24 (11.3%)

Those SE depressive showing either depressive or hyperthymic temperament were compared with patients with neither type of affective temperamental dysregulation

Table 5. Hamilton-D factors in SE depressives with and without affective temperaments

	SE with temperament ($n = 104$)	SE without temperament ($n = 109$)	P
Anxiety/somatization	1.11	0.95	<0.01
Weight	0.45	0.49	ns
Cognitive disorders	0.66	0.46	<0.001
Diurnal variation	1.00	0.90	ns
Motor retardation	1.77	1.74	ns
Sleep disorders	0.90	0.87	ns
Total HAM-D	21.96	19.60	<0.01

(Table 3). Hyperthymics had a significantly higher percentage of males than the two other subgroups; whereas those with depressive temperament showed a significantly lower mean age and age at onset. Patients with both types of temperaments also showed a greater severity of the HAM-D total score.

Combining the two groups having temperamental dysregulation (both depressive and hyperthymic) and comparing against the group without such dysregulation (Table 4), we found that SE associated with these temperaments was significantly younger at index evaluation, had earlier onset, and was more likely to arise from a bipolar familial background.

Our data further reveal that SE without temperamental dysregulation has milder depression with less anxiety-somatization and psychotic features (Table 5). Finally, despite similarity in family history for major depression these patients were significantly less likely to come from a bipolar background.

The 109 SE Patients *Without* Affective Temperamental Dysregulation were Finally Divided by Family History for Mood (Unipolar) Disorders

Those without such history had comparable rates of melancholia (50.0% vs 42.7%) and stressors (70.7% vs 61.8%) a significantly higher percentage of mood congruent psychotic features (14.7% vs 2.7%, $P < 0.05$), as well as significantly higher HAM-D total score (21.03 vs 18.95, $P < 0.05$), and a nonsignificant tendency towards chronicity (30.7% vs 20.6%).

Discussion

Since Angst (1973) delineated bipolar and unipolar forms of mood disorders, recurrence has been considered one of the fundamental features of these disorders. This concept has been upheld in the catamnestic study (Angst 1978). Goodwin and Jamison (1990), in their encyclopedic synthesis of the world literature, concur. Thus, SE depressions without further recurrence have not been well characterized in the literature. In particular, it is uncertain if they constitute a distinct entity. Although some authors, notably Weissman (1979), have questioned the validity of what was once termed "involutionial melancholia," the existence of late-onset, isolated yet prolonged agitated and delusional episodes of major depression (often triggered by stressors in male or female subjects with a low family loading for mood disorders but frequently with a subtle age-related "physical" component) has been debated (Pichot and Pull 1981) since Kraepelin's (1896) description of such a disorder.

The distinction between such a protracted depressive episode occurring once in the lifetime of the patient, and the first episode of a recurrent unipolar or bipolar disorder represents a critical prognostic point in order to optimize prognosis and clinical management. Dreyfus (1907), who had conducted a catamnestic study of Kraepelin's original case material, could not document major differences in the outcome of involutional cases from their earlier-onset (manic-depressive) counterparts, thereby casting doubt on the validity of a late-onset variety of mood disorders. Kraepelin (1921) concurred, and the concept of involutional melancholia suffered a slow death in world psychiatry (Pichot and Pull 1981). However, it appears to be reborn in different grab as the DSM-III-R (1987) single-epsiode subtype of major depressive disorder. This manual, widely, makes no reference to age at onset, and raises the possibility of recurrence. The main validation for single-episode subtype thus far has come from a Canadian study by Bland et al. (1986), who demonstrated significantly less family history for mood disorder compared with recurrent major depression; this, however, could reflect later age of onset where SE depressions are most common (Musetti et al. 1989).

The role of age at Onset in Subclassifying SE

When compared with 342 recurrent depressives of the same study cohort, SE patients showed a higher percentage of males, significantly higher mean age at onset and age at first hospitalization; as well as a significantly higher percentage showing a chronic denouement, and of stressors before the index episode; a lower rates of "endogenous" features; and less frequent lifetime suicide attempts. The later age at onset, the more frequent chronic course, the higher incidence of stressors, and the higher percentage of males found by us in SE patients when compared with recurrent depressions is in general agreement with previous observations, including Kraepelin's characterization of involutional melancholia. That lifetime suicide attempts were less frequent could be readily explained in terms of the shorter duration of illness in nonrecurrent depression. The lesser severity could be explained in part by the fact that in our patients co-morbidity with other mental disorders, as well as concomitant physical disorders, were excluded by study entry criteria; the latter might have exerted pathoplastic impact on the late-onset group. On the other hand, patients with SE did not differ on the basis of family history from recurrent unipolars.

To further characterize SE depression, we took into account the probability that to a certain extent early-onset depression could develop into a recurrent depres-

sive disorder. Patients with SE were, therefore, analyzed according to age at onset. These two subgroups showed differences in terms of age and age at first hospitalization, both influenced in part by how they were defined. The depressive temperament had a significant association with early-onset, as well as higher frequency of suicide attempts. The comparison of these two subgroups of SE with recurrent unipolars revealed the intermediate position of early-onset SE between late-onset "pure" SE and recurrent unipolars. Early-onset SE patients appeared to be closer to recurrent patients rather than to late-onset SE as far as suicide attempts and depressive temperament.

Thus, SE patients may be separated from recurrent depressives in terms of higher male percentage, higher mean age, later age at onset, higher percentage of chronic course, higher percentage of stressors before the index episode, and lower rate of family history for bipolar disorder. However, it might be considered that early-onset SE depression, especially when preceded by a depressive temperament, represents a first episode rather than a "single" episode. Therefore, the "real" SE subgroup should mainly comprise those patients showing a later onset of the illness. These patients, different in terms of higher chronicity and stressors, lower rate of suicide attempts and significantly lower percentage of depressive temperament, should be considered separately from recurrent unipolars as well from early-onset SE depressives. In fact, the comparison between early-onset single-episode and recurrent depression revealed certain features which would increase the likelihood of further recurrences in this subgroup of 83 subjects with SE. Prospective follow-up is needed to verify this.

As regards prognostic indicators, it is noteworthy that the comparison between SE with age at onset before and after 45 demonstrated significantly higher rates of depressive temperament and suicide attempts in the former group. This finding supports previous observations by us (Musetti et al. 1989) of a correlation between early-onset and depressive temperament in unipolar MDE and seems to indicate that the depressive temperament in subjects with SE is predictive of more severe depression with early-onset, high rates of recurrence and risk for suicide attempts. These findings are reminiscent of Winokur's (1979) suggestion on the existence of young depressive with "personality disturbances" that can be contrasted with later-onset "purer" depressives.

These considerations place the early onset subgroup of SE depressives closer to recurrent unipolar depressives, and permits the separation of this subgroup from the other 130 patients with late-onset SE, which more closely resemble those initially described by Kraepelin as "involutional melancholia" and having greater likelihood of remaining an isolated – albeit protracted – episode in the life history of the sufferer. However, the resemblance appears to be in the evolution of the episode (precipitated with tendency for chronicity) rather than in its clinical characteristics. Indeed, a recent reanalysis (Berrios 1991) of Dreyfus' (1907) original data suggests that Kraepelin's pupil may have understated the unfavourable outcome of late-onset depressives.

Temperament, Stressors and Chronicity

We found older index age, later age at onset and age at first hospitalization in SE patients with stressors preceding the onset of the index episode, in agreement with previous observation (Cassano et al. 1989) on the triggering role of stressors in late-onset unipolar disorders, whereas bipolar and early-onset unipolar depression are associated with a greater familial-genetic loading. In SE depressives the comparison by family history for mood disorders showed a greater severity on the HAM-D and a higher, though not significantly, percentage of depressive temperament in patients with family history. The percentage of hyperthymic temperament was higher in those having had a stressor, whereas the depressive temperament was higher in subjects without stressors, though these differences were not significant.

The tendency to protracted course, however, did emerge as a characteristic of SE depression, especially in late-onset patients. The comparison of SE depressives subdivided by the presence or absence of chronicity did not show relevant differences. Establishing as limit of chronicity the mean duration of the episode (1.6 years), the subgroup with shorter duration had a significantly greater rate of hyperthymic temperament that, as in previous observations (Cassano et al. 1992), does suggest some protection not only from depressive episodes but also from the tendency to chronicity. We speculate that a higher tendency to be exposed to stressors in hyperthymics – perhaps based on novelty-seeking – and a lower one in depressive temperament, might be differentially at risk for life events and subsequent episodes. Moreover, to continue this line of extrapolation, the hyperthymic temperament may, for a certain period, prevent or delay the appearance of a depressive episode, whereas the depressive temperament seems to be associated with a much lower threshold for age at onset of the MDE with relatively minimal provocation by stressors. A higher tendency to switch from depression back into hyperthymia could in turn explain the lower mean duration of depressive episode in hyperthymics. These considerations are in line with the suggestion by Young et al. (1989), of better outcome in geriatric depressives with high sensations-seeking (one of the defining items of the hyperthymic temperament).

Early-Onset SE as a Precursor of Recurrent Mood Disorders

Previous analyses on our entire data set of 687 major depressives (Cassano et al. 1992) suggested that hyperthymic and depressive temperaments could serve to characterize distinct subtypes of MDE. The present data further document the role of depressive temperament in favouring earlier onset and higher rate of suicide attempts. In addition, the two groups with hyperthymic and depressive temperament had a significantly higher total HAM-D score and were distinguishable from the group with no pre-existing affective temperamental dysregulation as far as family history for bipolar disorder, which

were present in 12.5% and 6.3%, respectively, in the hyperthymic and depressive temperament subgroup, whereas none of the SE depressives without affective temperament (and late onset) reported family history for bipolar disorder. This finding contrasts with the family history for unipolar MDE which did not differ between the three groups. Therefore, from a "genotypic" standpoint, late-onset depressive episodes are unipolar in nature. This conclusion is concordant with Pichot and Pull (1981). On the other hand, SE with pre-existing temperamental dysregulation (having a significantly higher family history for bipolar disorder, a greater severity of the symptomatology with an earlier onset and higher rate of suicide attempts and a male-female ratio close to bipolar patients) suggests the likelihood of depressive recurrence. "Genotypically" they appear heterogeneous, having features of both unipolar and bipolar disorders and some might represent earlier and softer expressions of a bipolar diathesis (Akiskal 1983b, Akiskal and Akiskal 1988, 1992). These considerations are in line with Stenstedt's (1959) conclusion about the heterogeneity of single-episode depressives followed up over time.

Late-Onset SE sui Generis

Half of our study population had no pre-existing temperamental dysregulation, had late-onset, a greater tendency for chronicity and absence of family history for bipolar disorder – though having family history for MDE similar to the other subgroups. As in the Pichot and Pull study (1979), these patients are symptomatologically indistinguishable from other depressives, especially after controlling for the pathoplastic effect of age. These patients nonetheless seem to share evolutive features of Kraepelin's involutional melancholia (1896). That our patients are not as ill as his involutional melancholics might be due to the fact that our population is largely outpatient and without comorbidity (especially without physical illness) that was excluded by protocol. Overall, our data still suggest that a late-onset single episode variety of depression might represent a distinct entity that can be characterized as the "purest" expression of unipolar depression. The resemblance to Kraepelin's involutional category then pertains more to evolutive features, i.e. late onset precipitated protracted depression, than to symptomatological uniqueness regarding agitated delusional melancholia.

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