Onset of Depressive Episodes Is Faster in Patients With Bipolar Versus Unipolar Depressive Disorder: Evidence From a Retrospective Comparative Study

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Objective: Depressive episodes can have a very fast onset (< 1 hour) or start very slowly (> 1 month). This interesting aspect, pointing to different neurophysiological pathomechanisms, has not been systematically evaluated so far. The aim of this study was to describe speed of onset of depressive episodes in a consecutive sample of patients with at least 1 depressive episode and to investigate potential differences between patients with major depression versus bipolar affective disorders concerning this variable.

Method: We examined 158 consecutive adult patients with major depression (N = 108) and bipolar disorder (N = 50) diagnosed according to criteria of the *International Statistical Classification of Diseases*, 10th revision, by applying the structured Onset-of-Depression Inventory. Patients with acute critical life events preceding the onset were excluded from final analyses. Data were collected between December 2001 and January 2007.

Results: There was a significant positive association between speed of onset of the present depressive episode and that of the preceding depressive episode ($\rho = 0.66$, $p < .001$). Patients with bipolar disorder developed full-blown depressive episodes significantly faster than patients with major depression ($p < .001$): Whereas depressive episodes began within 1 week in 58% of patients with bipolar disorder, this was the case in only 7.4% of patients with major depression.

Conclusion: Intraindividually, the speed of onset of depression is similar across different episodes. In the absence of acute critical life events, fast onset of depressive episodes (within 1 week) is common in bipolar disorder but rare in major depression. This aspect might be useful to identify depressive episodes occurring within a bipolar affective illness and might characterize a subgroup of patients with a distinct neurobiology.

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It is common clinical experience that there is a broad variation in the speed of onset of depressive episodes. On the one side of the spectrum, there are patients who develop a full-blown depressive episode within 1 hour; on the other side are patients in whom the depressive episode develops slowly over months. It can be expected that these patients differ concerning neurobiological mechanisms involved in the pathogenesis of these episodes.

It is of interest in this context that the speed of depressive episodes appears to be more rapid in patients with bipolar affective disorder (BD) compared to those with major depression (MD). Especially rapid switches between depressive and manic states are not uncommon in BD, but also the onset of depression from the euthymic state might be more rapid, as suggested by a retrospective and comparative study.[1] If this is commonly the case, the speed of onset might be helpful to identify depressive episodes occurring within MD versus BD. The early identification of patients with BD remains a clinically highly relevant and unsolved problem, as up to 45% of patients with BD

initially present with a major depressive episode.[2] This knowledge could help to identify those patients who are at risk for developing mania and thus might benefit from an early mood-stabilizing therapy or at least should be more carefully observed. Up to now, in the absence of prior manic or hypomanic episodes, there are no indicators allowing a reliable diagnostic classification of depressive episodes.[3] Some clinical aspects, such as family history of major depression or mania,[4–7] psychosis during the index depressive episode,[6,8–10] atypical and neurovegetative symptoms (like hyperphagia and hypersomnia),[11–13] melancholic symptoms,[14–16] and familial variation in episode frequency[17] have been proposed, but the literature is not consistent (for review, see Benazzi[18]).

Surprisingly, the speed of onset of depressive episodes has, to our knowledge, not been systematically studied up to now. Only one study gives quantitative information about differences between patients with BD and those with MD regarding speed of onset of depressive episodes: In this study of Tunisian inpatients, sudden onset of depressive episodes was present in 44.8% of patients with BD but only in 15.9% of patients with recurrent depressive disorders.[1]

Therefore, we developed a structured clinical inventory—the Onset-of-Depression Inventory (ODI)—designed to assess the speed of onset of depressive episodes.

The first question that had to be answered was whether the speed of onset of depressive episodes is a stable individual characteristic over different episodes. This should be the case if the speed of onset reflects stable interindividual differences in pathophysiological and possibly genetic aspects. Therefore, we correlated the speed of onset of the present depressive episode with that of the preceding episode.

Our principal hypothesis was that the speed of onset would be faster in BD than in MD.

METHOD

Subjects

Consecutive patients (N = 215) were recruited at wards in the Department of Psychiatry (Ludwig-Maximilians-University, Munich, Germany), in the outpatient clinic for patients with bipolar affective disorders at this institution, and in a study center for clinical trials at Nuremberg associated with the above-mentioned Department of Psychiatry. In the latter center, patients were drawn from a clinical trial of mild depression in the context of primary care. Data were collected between December 2001 and January 2007.

The inclusion criteria for this open, retrospective, cross-sectional study were a minimum age of 18 years; the ability to give written informed consent; and a diagnosis of bipolar affective disorders, depressive episodes in the context of a major depressive disorder, or recurrent depressive disorder. Exclusion criteria were dysthymia, double depression, or other persistent depressive disorders without major depressive episodes; duration of the present episode of more than 2 years (this was the case in 13 patients); acute suicidality; addiction to alcohol or drugs; drug-induced depressive disorders; psychotic disorders; severe somatic diseases, especially acute life-threatening ones; or dementia.

The psychiatrists' diagnosis was based on the *International Statistical Classification of Mental Disorders,* 10th revision (ICD-10)[19] criteria, because ICD-10 diagnoses are required at German hospitals. In the subsample of patients from Nuremberg (N = 87), the diagnosis was additionally based on a fully structured clinical interview, the Composite International Diagnostic Interview (CIDI),[20] according to DSM-IV criteria. In this context, a German computer-administered form (DIA-X)[21] was applied, based on CIDI version 1.1.[20]

After complete description of the procedures to the subjects, written informed consent was obtained according to the guidelines of the Declaration of Helsinki. The ethics review committee (Medical Faculty; Ludwig-Maximilians-University, Munich, Germany) had approved the study before its starting.

Onset-of-Depression Inventory (ODI)

The velocity of onset of present, preceding, and first depressive episodes was assessed using the ODI.

The ODI is a structured patient interview registering, first, the presence or absence of manic or hypomanic episodes known from the patients' anamnesis. The next ODI section focuses on the onset of the current depressive episode.

The patient was asked to give information about the date of onset and the length of time until full-blown depression had developed (using 9 categories: 0 to 30 minutes; more than 30 to 60 minutes; more than 1 to 3 hours; more than 3 to 24 hours; more than 1 to 3 days; more than 3 to 7 days; more than 1 to 4 weeks; more than 1 to 4 months; more than 4 months). Furthermore, the symptoms with which the current depressive episode started were assessed (11 categories are given: depressive mood; joylessness; loss of interest; increased fatigue; sleep disorders; daily fluctuations of mood; loss of energy; changes of appetite; loss of libido; disturbances of concentration; suicidality). Additional symptoms (like anxiety) could be coded, too. Acute critical life events (type and date) in the 14 days preceding onset of depression were documented. Preceding treatments including medication, electroconvulsive therapy, and psychotherapy and their changes were also documented.

In addition to the present episode, the onset and end of the preceding and the first depressive episode (in case of patients with recurrent depressive disorders) were characterized by the ODI.

Table 1. Demographic and Clinical Characteristics of 158 Patients With Major Depression or Bipolar Affective Disorders

Variable	Major Depression (N = 108)	Bipolar Affective Disorders (N = 50)	p
Age, mean ± SD, y	47.62 ± 14.13	48.89 ± 11.71	.58[a]
Sex, male/female, N (%)/N (%)	40 (37)/68 (63)	26 (52)/24 (48)	.08*[b]
Inpatient/outpatient, N (%)/N (%)	10 (9.3)/98 (90.7)	26 (52.0)/24 (48.0)	< .001***[b]
HAM-D-17 total score, mean ± SD	14.20 ± 5.48	11.74 ± 5.10	.04**[c]
Number of depressive episodes, mean ± SD	2.06 ± 0.81	2.80 ± 0.495	< .001***[c]
Duration of inpatient treatment for present depressive episode, mean ± SD, d	71.82 ± 19.98	85.85 ± 69.56	.71[c]
Duration of present depressive episode, mean ± SD, d	218.26 ± 170.89	155.13 ± 155.26	.06*[c]

[a]By t test for independent sample comparison (2-tailed).
[b]By χ^2 test for 2 independent samples (2-sided).
[c]By Mann-Whitney U test (2-tailed).
*p ≤ .10 (unadjusted significance levels).
**p ≤ .05 (unadjusted significance levels).
***p ≤ .001 (unadjusted significance levels).
Abbreviation: HAM-D-17 = Hamilton Rating Scale for Depression, 17-item version.

The following additional clinical variables were collected: number of depressive episodes, psychiatric comorbidity, total score on the 17-item Hamilton Rating Scale for Depression (HAM-D-17),[22] duration of depressive episodes, and duration of inpatient treatment.

The ODI interviews were conducted by 4 clinical and mood disorder research physicians with several years in practice (B.H.-T., F.S., M.S., and W.S.) and 1 clinically experienced psychologist (A.-C.B.). The ODI interviews were conducted after stabilization and improvement of the depressive syndromes.

Statistical Analysis

The results of the interviews were imported into the statistical program SPSS, version 12.0 (SPSS Inc., Chicago, Ill.). We computed Spearman-Brown correlation coefficients between speed of onset of the present and the preceding depressive episode.

Differences between patients with MD and patients with BD in continuous, normally distributed variables (like age) were tested by t tests for independent sample comparison. If variance homogeneity was not given (Levene test, $p \leq .05$), t tests with corrected degrees of freedom have been computed. Medians for speed of onset of depressive episodes were compared with the nonparametric 2-sample Mann-Whitney test. Proportions were compared with Pearson χ^2 tests, which were regarded to be valid if more than 80% of the cells had expected values above 5. If this was not the case, Fisher exact tests were applied for comparing 2 dichotomous variables. If necessary, an analysis of covariance design was applied to control for the effects of moderator variables on the dependent variables.

In order to determine valuable cutoff scores for the discrimination between patients with MD and BD by speed of onset of the present depressive episode, receiver operating characteristic (ROC) curves were construed. The correspondent area under the curve (AUC) value and a table summarizing the coordinates of the ROC curve were therefore calculated.

All tests were 2-tailed, and $p < .05$ determined statistical significance.

RESULTS

Demographic and Clinical Characteristics

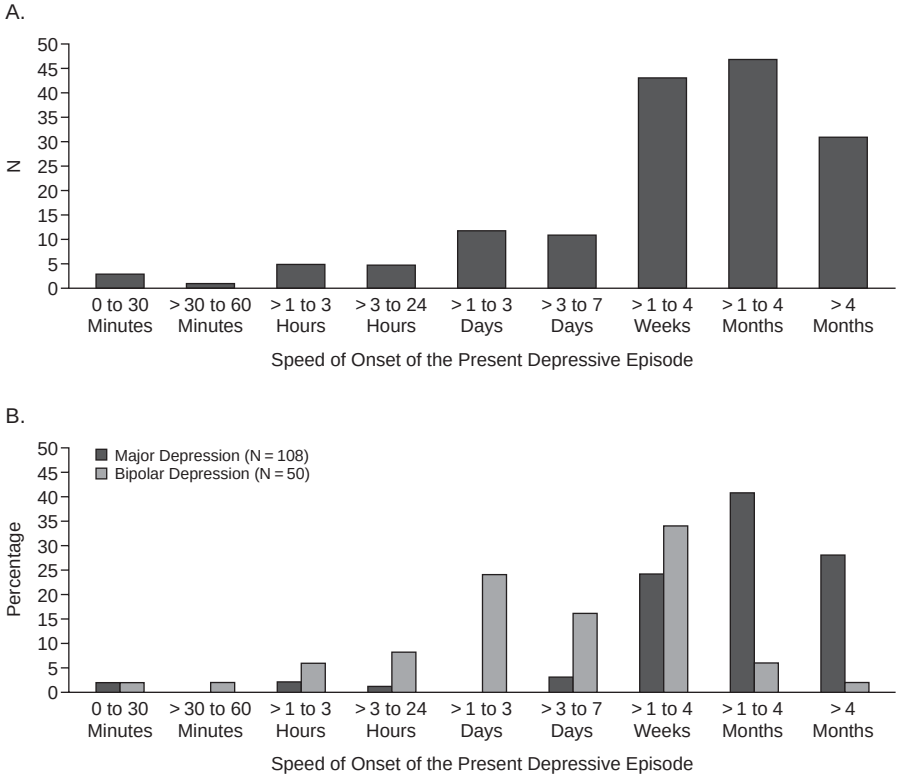
Thirty-three of 141 patients with MD (23.4%) and 24 of 74 patients with BD (32.4%) were excluded from further analyses because of acute critical life events in the 2 weeks before depression onset. The most frequent types of self-reported acute critical life events were daily stressors (e.g., annoying telephone calls, relocation) (MD: N = 9 [27.3%]; BD: N = 9 [37.5%]), separation from partners and interpersonal conflicts (MD: N = 10 [30.3%]; BD: N = 5 [20.8%]), work-related critical life events (e.g., loss of workplace) (MD: N = 6 [18.2%]; BD: N = 4 [16.7%]), death of close relatives (MD: N = 5 [15.2%], BD: N = 2 [8.3%]).

Demographic and clinical features of the remaining patients with BD versus MD are presented in Table 1. From the patients with MD, 80 (74.1%) had recurrent depressive disorders. Forty-eight (96.0%) of the patients with BD had more than 1 depressive episode.

Association Between Speed of Onset of Depressive Episodes and Clinical Variables

Whereas severity of depression in the present episode as assessed by the HAM-D-17 total score was not significantly associated with the speed of onset of the present depressive episode ($\rho = 0.20$; $p = .08$), there was a significant positive correlation between the speed of onset of the present depressive episode and its duration ($\rho = 0.27$; $p = .02$). Inpatients were found to have a significantly lower median speed of onset of the present depressive

Figure 1. Frequency Distribution of the Speed of Onset of the Present Depressive Episode in (A) the Total Sample (N = 158) and (B) Patients With Major Depression (N = 108) and Bipolar Affective Disorder (N = 50)



episode (1–4 weeks) than outpatients (1–4 months) (Mann-Whitney U test: $Z = -3.70$; $p < .001$). In the next step, we asked whether, as assessed by the ODI (see *Onset-of-Depression Inventory* section), the initial symptoms of fast onset of depression (≤ 3 days) were different from those of slow onset of depression (≥ 1 month). Such differences were only found for 2 symptoms (loss of libido and suicidality): Whereas 22 of 26 patients with fast onset of the present depressive episode (84.6%) suffered from loss of libido, this was the case in only 36 of 78 patients with slow onset of depression (46.2%) ($\chi^2 = 11.69$; df = 1; $p = .001$). Similarly, suicidality was significantly more frequent in patients with fast onset of the present depressive episode (11/26; 42.3%) than in patients with slow onset of depression (12/78; 15.4%) ($\chi^2 = 8.21$; df = 1; $p = .004$).

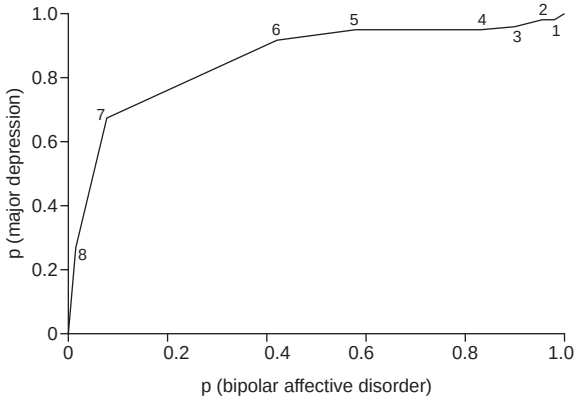
Characteristics of the Onset of Depressive Episodes

Association between speed of onset of the present depressive episode and that of the preceding one was highly significant ($\rho = 0.66$, $p < .001$; patients with MD: $\rho = 0.52$, $p < .001$; patients with BD: $\rho = 0.61$, $p < .001$). The correlation coefficients in patients with MD and patients with BD were comparable (Fisher r-to-z transformation; $z = -0.69$; $p = .49$).

Figure 1A demonstrates the frequency distribution of speed of onset of the present depressive episode of all patients. Patients with MD (N = 108) had a median speed of onset of the present depressive episode of 1 to 4 months; in contrast, the patients with BD (N = 50) had a much shorter median onset of the present depressive episode of 4 to 7 days. The corresponding group difference was significant ($Z = -7.46$; $p < .001$). Figure 1B gives more detailed information about the speed of onset of the present depressive episode in patients with MD versus BD: whereas the present depressive episode began within a week in 29 (58%) of 50 patients with BD, only 8 (7.4%) of 108 patients with MD had an onset of the present depressive episode that was as rapid.

Receiver operating characteristic analysis confirmed the above-mentioned results and revealed that, overall, patients with MD and those with BD can be well separated by speed of onset of the present depressive episode (AUC = 0.86, 95% CI = 0.797 to 0.92, $p < .001$; Figure 2). A cutoff score of 1 month discriminated these patient groups very well: 46 (92.0%) of 50 patients with BD were characterized by faster onset, 74 (68.5%) of 108 patients with MD by slower onset of the present depressive episode.

Figure 2. Discrimination Between Patients With Major Depression (N = 108) and Patients With Bipolar Affective Disorder (N = 50) by Speed of Onset of the Present Depressive Episode: Results of Receiver Operating Characteristic Analysis[a,b]



[a]The axes reflect the probabilities (p) of patients' with MD/BD having a slower onset of the present depressive episode than indicated by the correspondent cutoff score (e.g., 1 month; MD: 68.5%; BD: 8%).
[b]The cutoff scores were as follows: 1 = 30 minutes; 2 = 1 hour; 3 = 3 hours; 4 = 1 day; 5 = 3 days; 6 = 1 week; 7 = 1 month; 8 = 4 months.
Abbreviations: BD = bipolar affective disorder, MD = major depression.

Of the patients with BD (N = 50), 7 (14.0%) switched from mania into the present depressive episode. The other patients with BD were in an euthymic state before the present depressive episode. If bipolar patients with switch events are excluded from analysis, differences between MD and BD patients in speed of onset of the present depressive episode were still significant (Mann-Whitney U-test: $Z = -6.99$; $p < .001$).

DISCUSSION

The speed of onset of depressive episodes is a relevant clinical aspect that has largely been neglected in clinical research so far. The finding that, within individual patients, different depressive episodes show a similar speed of onset suggests that this is a stable characteristic, possibly driven by endogenous neurobiological mechanisms. In both MD and BD patients, the speed of onset of the present and the preceding depressive episode were positively correlated.

The main hypothesis of this study was that the speed of onset of depressive episodes would be faster in BD than in MD patients. This hypothesis was clearly confirmed. Fast onset of the depressive episode (within 1 month) was more common than slower onset (> 1 month) in patients with BD (92% vs. 8%, respectively); the opposite relationship (31.5% vs. 68.5%) was found for patients with MD. The observed difference in speed of onset does not merely reflect differences in the frequency of preceding acute critical life events (like death of the partner) that might lead to rapid onset of episodes: Both groups did not significantly differ in the percentage of such events, and the obtained differences remained after excluding patients with acute critical life events.

In the literature, we found only 1 retrospective comparative study reporting about the onset of depressive episodes in patients with MD and BD[1]: In 44.8% of patients with BD, but only in 15.9% of patients with recurrent depressive disorders, sudden onset was found. These results are similar to those in our study, in which depressive episodes were found to develop in 42% of patients with BD within 3 days, as opposed to 4.7% of patients with MD.

In 7 of the patients with BD, the onset of the present depressive episode resulted from a switch from a preceding manic episode. Even after excluding these patients, the differences between patients with MD and patients with BD in speed of onset of the present depressive episode remained statistically significant.

An exploratory analysis revealed that slower onset of the present depressive episode was associated with longer phase duration. Outpatients had a slower onset of depression than inpatients. The result that suicidality was more frequent in patients with faster onset is of potential clinical significance but surely needs replication in a larger sample.

We have also addressed the question of whether patients with unipolar versus bipolar depression differ not only in speed of onset of depressive episodes but also regarding other clinical variables (like number and length of depressive episodes). Patients with unipolar depression had fewer episodes than the bipolar patients, with the difference being significant at the 1% level. The higher number of recurrences is among the basic, distinguishing features of bipolar disorder compared to major depressive disorder.[23] Our finding that bipolar depressive episodes showed a statistical tendency to be briefer in duration than unipolar ones has quite consistently been reported in previous studies.[11,15,24–27] This difference probably points to different pathomechanisms in patients with unipolar and bipolar depression, because it was found not only in patients who had been treated before referral to the tertiary care center where patients had been enrolled[26] but also in patients with broadly defined affective disorders who had not received therapy for their index episode before study entry.[25] Thus, this difference does not seem to be restricted to inpatients and cannot be explained only by treatment differences.

There are some limitations of the present study: First, because the speed of onset of depressive episodes tends to catch endogenous pathophysiological aspects, external triggers have to be controlled for. Doing so requires assessing acute critical life events. However, the definition and valid assessment of such life events are notoriously

difficult.[28] Objective and subjective quantitative and qualitative aspects of a certain life event can differ considerably. These problems do not seem to have biased our results, however, because the number of acute critical life events according to patients' reports was similar in BD and MD patients, and depressive episodes with identifiable preceding acute critical life events were excluded from analysis. Additionally, we did not control for medication effects. Thus, we cannot exclude the possibility that different compliance behavior in both groups or withdrawal effects of antidepressant medication may have influenced our data.

Another limitation of this study is that the interviewers were not blind regarding diagnosis of the patients, and the possibility cannot be excluded that, in some cases, this lack of blinding may have influenced the results of the study. Moreover, most patients were interviewed when they were clinically improved. They were asked to recall events occurring when the present and the previous episode started. In some patients, these events dated back many months, thus reducing the validity of the patients' reporting.

Further limitations were as follows: Only about one half of the subjects received a diagnosis via a structured clinical interview. The study was retrospective and not blind. The subjects were assessed in different clinical states, and the ODI has not been validated so far.

Within these constraints, this study clearly indicates that the speed of onset of depressive episodes is a relevant clinical aspect that should be considered more carefully in future studies. For clinicians, it is important to know that a rapid onset of a certain depressive episode (within 1 week) is a common finding within BD but much less so within unipolar depression. Speed of onset may also be helpful to define pathophysiologically more homogeneous subgroups within MD and BD. Interesting questions for future research are whether the same group differences can be seen in time to remission from depressive episodes, or to what extent patients with rapid versus slow onset differ concerning treatment response and genetic aspects.

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