One-Year Course and Predictors of Outcome of Adolescent Depression: A Case-Control Study in Finland

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Background: Clinical studies on the outcome of adolescent depression beyond treatment trials are scarce.

Objective: To investigate the impact of characteristics of the depressive episode and current comorbidity on the 1-year outcome of depression.

Method: A sample of 174 consecutive adolescent psychiatric outpatients (aged 13 through 19 years) and 17 school-derived matched controls, all with unipolar depressive disorders at baseline, were reinterviewed for DSM-IV Axis I and Axis II disorders at 12 months. The study was conducted between January 1998 and May 2002.

Results: The outpatients had equal recovery rate and episode duration but shorter time to recurrence than the controls. Among the outpatients, Axis II comorbidity predicted shorter time to recurrence ($p = .02$). Longer time to recovery was predicted by earlier lifetime age at onset for depression ($p = .02$), poor psychosocial functioning ($p = .003$), depressive disorder diagnosis ($p \leq .05$), and longer episode duration by study entry ($p = .001$), with an interaction between episode duration and depressive disorder diagnosis ($p = .04$).

Conclusions: Characteristics of depression generally predicted the outcome better than comorbidity. Axis II comorbidity has prognostic value in adolescent depression.

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Comprehensive reviews conclude that the mean episode duration of adolescent major depressive disorder (MDD) is 4 to 9 months among clinically referred youths, that recovery rates vary between 35% and 90%, and that the likelihood of recurrence is high.[1,2] In naturalistic studies comprising less selected study populations than treatment trials, various comorbid psychiatric disorders and poor psychosocial functioning or depression severity at study entry are among the most consistently reported psychopathologic predictors of less favorable prognosis of depression.[3–8] These studies, however, are methodologically heterogeneous, and rarely comprise a wider spectrum of unipolar depressive disorders than MDD.[6] Moreover, pure adolescent-aged clinical populations among prospective studies applying diagnostic interviews at all measurement points are scarce.[8] We describe the 1-year course and identify diagnostic and psychopathologic predictors of outcome of unipolar depressive mood disorders in consecutively referred adolescent psychiatric outpatients and matched school-based controls.

METHOD

The Adolescent Depression Study

The subjects of this study were drawn from the study population of the Adolescent Depression Study (ADS), which is a naturalistic, clinical follow-up study on adolescent depressive mood disorders. The ADS study population consisted of 2 samples with current depressive mood disorders: one of consecutive adolescent psychiatric outpatients (N = 218) and the other of school-attending age-matched and sex-matched controls (N = 200). The outpatient clinics and the schools were located in the area of Peijas Medical Health Care District, which serves approximately 210,000 inhabitants and comprises the cities of Vantaa and Kerava within the Helsinki metropolitan area of southern Finland. Data were obtained by interviewing the adolescents themselves and collecting additional background information (e.g., data from family and school) from the clinical records. The ADS study population has been described in detail elsewhere,[9,10] and here a briefer account follows. The study protocol has been accepted by the ethics committees of Helsinki University Central Hospital and Peijas Medical Health Care District. After the baseline evaluation (T1), both the outpatients and controls were reevaluated approximately 1 year later (T2). The median time interval between T1 and T2 was 59.5 weeks (interquartile range [IQR], 57.0–63.0 weeks) in the clinic group and 57.0 weeks (IQR, 54.0–60.5 weeks) among the controls, the time difference being statistically significant (Mann-Whitney U, $z = -2.49$, $p = .01$).

Subjects

The clinic group of ADS was initially screened from 774 consecutive admissions to the Peijas Medical Health Care District clinics for adolescents between 1998 and 2001.[9,10] The exclusion criteria were age below 13 or over 19 years, mental retardation, insufficient knowledge of the Finnish language, or admission including no individual appointments. In all, 660 subjects (85.3%) were eligible for screening, and 373 of them (56.5%) were screen positives. Of the screen positives, 221 (59.2%) agreed to participate in the study and were then interviewed. Almost all of the interviewed subjects (N = 218) had an ongoing episode of either unipolar or bipolar depression at T1 and were recruited to the study. Adolescents refusing to participate were similar to the study subjects in terms of age, sex, and parental socioeconomic status, while they tended to have lower screening scores.[9,10]

The school controls were drawn from the same geographic area as the clinic group in spring 2002 by selecting an age-matched and sex-matched random sample of students with a comparable education level to the outpatients.[9] The exclusion criteria were recruitment to the clinic group and insufficient knowledge of the Finnish language. Moreover, 37 adolescents refused to participate and 6 subjects were not reached. In cases of exclusion (N = 4) or refusal, the next matching candidate was picked from the student list. In all, 200 controls were interviewed, of whom 22 had ongoing unipolar or bipolar depressive episode at T1.[9]

Of the entire ADS study population,[9] those with (1) unipolar depression at T1 (N = 203 outpatients, N = 20 controls) and (2) diagnostic interview data available at T2 (N = 174 outpatients, N = 17 controls) were included in this study (N = 191). Those lost to attrition between T1 and T2 (N = 29 outpatients, 14.3%; N = 3 controls, 15.0%) did not differ from those retained to the follow-up in terms of the central sociodemographic (sex: $\chi^2 = 0.15$, $df = 2$, $p = .70$; age: $z = -0.53$, $p = .60$) and psychopathologic factors (depressive disorder diagnosis: $\chi^2 = 2.54$, $df = 4$, $p = .64$; episode duration by T1: $z = -0.46$, $p = .65$; any psychiatric comorbidity: $\chi^2 = 0.001$, $df = 2$, $p = .98$; Global Assessment of Functioning (GAF) score: $z = -1.5$, $p = .88$), with the exception of lower parental socioeconomic status associating with drop-out ($\chi^2 = 23.6$, $df = 3$, $p < .001$).

Treatment

As the study was naturalistic, the outpatients received "treatment as usual" of clinically defined duration in a general adolescent psychiatric setting of Finnish secondary health care. Approximately half (N = 90, 51.7%) of the 174 outpatients were prescribed antidepressant medication, mostly selective serotonin reuptake inhibitors (N = 87; 50.0%), during the 1-year follow-up time. Eighty-nine outpatients (51.1%) received some kind of individual psychotherapy, and 85 (48.9%) received at least 1 session of family counseling. Combined treatment was received as follows (data available for 170 outpatients): medication and individual psychotherapy (N = 49, 28.8%), medication and family counseling (N = 40, 23.5%), individual psychotherapy and family counseling (N = 45; 26.5%), and all 3 (N = 25, 14.7%). At T2, 44.8% (N = 78) of the outpatients were continuing the treatment. Among those who had completed treatment by T2 (N = 96), the median duration of treatment was 233 days (IQR, 125–323 days) and the median number of treatment appointments was 12 (IQR, 8–18.5). The control sample served as a model of the "natural course" of depression and comprised subjects not initially referred to mental health services. The controls were, however, free to contact health care at any time during the study period, and by the 1-year follow-up interview, 9 controls (52.9%) had reported contact with adolescent psychiatric services.

Predictors—Baseline (T1) Characteristics

Diagnostic interviews and diagnostic definitions. The Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL)[11] was used to assess present and lifetime

episodes of *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) Axis I disorders. DSM-IV Axis II disorders were assessed with the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II).[12] The diagnostic interviews and the reliability data of the ADS study population are described in detail elsewhere.[9,10] Double depression was defined as preexisting dysthymic disorder with duration of at least 1 year prior to the onset of a superimposed major depressive disorder (MDD).[13] The category of minor depression comprised subjects with DSM-IV diagnoses of depressive disorder not otherwise specified (NOS) and adjustment disorder with depressed mood.[10]

The diagnoses of Axis II disorders also followed the DSM-IV guidelines so that a persistent and systematic pattern of behavior and emotional response had to be present prior to the onset of depressive episode.[13] According to DSM-IV, antisocial personality disorder is the only Axis II diagnosis with clear age limit, and the age of 18 years was required to make the diagnosis.[13] At T1, the Axis II diagnoses were distributed in the clinic group so that cluster B (13.3%) and cluster C (13.8%) were the most common categories, followed by mixed (11.9%) and cluster A (2.3%).[9] Similar distribution was observed among the controls except for cluster B category being more common than any other category.[9]

Definitions of time of onset, episode duration, remission, and recovery. Time of onset was identified as the time point when the minimum requirements for each DSM-IV diagnosis were simultaneously present. Probing questions were used to obtain the best possible accuracy. Unless the exact date was given by the respondent, information was collected to achieve an accuracy of 1 month. If this was not possible, the year of the event was noted. In data analyses, lifetime age at onset for depression was treated both as a continuous and as a dichotomized (childhood onset < 12 years vs. adolescent onset ≥ 12 years) variable. The variable *episode duration* indicates the duration of the index episode in weeks.

Major depressive disorder was defined as partially remitted if fewer than 5 and greater than 1 symptoms were present, and completely remitted if 1 symptom or no symptoms were identified for 2 weeks and less than 2 months.[14] Two months of 1 symptom or no symptoms (no depressed or irritable mood or anhedonia) was defined as recovery.[14,15] Recurrence was defined as a new depressive episode emerging after the beginning of recovery.[1]

Severity of depression and psychosocial functioning. Self-reported severity of depressive symptoms was assessed by using the sum-score (range, 0 to 63) of the 21-item Beck Depression Inventory (BDI-21).[16,17] Observer-reported severity of depressive symptoms was assessed by using the sum-score (range, 0 to 52) of the 17-item Hamilton Rating Scale for Depression (HAM-D-17)[18] rated by the interviewers during the diagnostic interviews.

Psychosocial functioning (Global Assessment of Functioning, GAF) was rated according to the DSM-IV Axis V definitions. In data analyses, the GAF score was used both as a continuous and as a dichotomous variable, with a cut-point of 60 indicating at least moderate impairment.[9,10]

Outcome Variables and Statistical Methods

Statistical Package for the Social Sciences (SPSS, Version 14.0)[19] was used for data analyses. For descriptive analyses, we applied χ^2, Kruskal-Wallis, and Mann-Whitney U tests for categorical and non–normally distributed numerical variables. Values of $p < .05$ were considered statistically significant. The descriptive statistics defining the characteristics of the course of depressive disorders were applied to both the clinic and the control group, and comparisons were made between the 2 groups.

For multivariable modeling, the main outcome variable was the diagnostic status of the depressive disorder (1 = recovery, 2 = persistent depression, 3 = recurrence during the study period) at the time of the 1-year follow-up diagnostic interviews. The 2 other outcome variables were time to recovery and time to recurrence. These multivariate analyses were performed for the clinic group only.

Univariate and multivariate analyses on the predictors of the diagnostic status of depressive disorder at T2 were conducted by logistic regression for bivariate outcome variables (persistent depression vs. recovery; recurrent depression vs. recovery) and by the Cox proportional hazards model for continuous outcomes of time to recovery and time to recurrence. Multivariate analyses were performed by using a fixed model including all the independent variables significant in univariate analyses, adjusted for age and sex. Odds ratios (ORs) or hazard ratios with their 95% confidence intervals (95% CIs) not including 1 were considered statistically significant.

RESULTS

Course of Depression: Clinic Group

A total of 41.4% (N = 72) of the adolescent psychiatric outpatients with any unipolar depressive disorder at baseline (T1) had recovered by the 12-month interview (T2) (Table 1). The majority of depressive disorder diagnoses at T2 comprised full criteria MDD, but the proportion of MDD in partial or full remission was also high (Table 1). Moreover, 4 subjects with partially remitted MDD continued to have full syndrome dysthymic disorder. When subjects with full remission were included among those recovered, the recovery rate was 44.8% (N = 78). Four adolescents (2.3%) with unipolar depression at presentation developed at least 1 manic or hypomanic episode during the follow-up and were diagnosed with bipolar disorder at T2 (Table 1).

Table 1. Characteristics of the Adolescent Depression Study Participants Who Had Unipolar Depressive Disorder at Baseline (T1) and Participated in the Diagnostic Interview at 12-Month Follow-Up (T2)[a]

	Clinic Group (N = 174)		School Control Group (N = 17)	
Characteristic	T1	T2	T1	T2
Sociodemographic characteristic				
Female	81.0 (141)	…	88.2 (15)	…
Age, mean (SD), y	16.4 (1.63)	…	16.2 (1.94)	…
Parental socioeconomic status[b]				
Working class	28.3 (49)	…	41.2 (7)	…
Lower middle class	38.7 (67)	…	52.9 (9)	…
Upper middle class	26.0 (45)	…	5.9 (1)	…
Depressive mood disorder diagnosis				
Recovered	0	41.4 (72)	0	52.9 (9)
Unipolar MDD				
Full criteria	81.6 (142)	26.4 (46)	52.9 (9)	17.6 (3)
Partial remission	2.9 (5)	19.0 (33)	0	5.9 (1)
Full remission	0	3.4 (6)	5.9 (1)	5.9 (1)
Dysthymic disorder	13.2 (23)	6.9 (12)	17.6 (3)	5.9 (1)
Dysthymic disorder + MDD	6.9 (12)	4.0 (7)	5.9 (1)	0
Bipolar depression	0	2.3 (4)	0	5.9 (1)
Minor depression	9.2 (16)	4.6 (8)	29.4 (5)	5.9 (1)
Current psychiatric comorbidity[c]				
Any	79.3 (138)	69.6 (71)	64.7 (11)	75.0 (6)
Any Axis I	74.1 (129)	58.8 (60)	52.9 (9)	50.0 (4)
Any anxiety disorder	57.5 (100)	43.1 (44)	41.2 (7)	50.0 (4)
Any substance use disorder	16.7 (29)	10.8 (11)	5.9 (1)	12.5 (1)
Any disruptive disorder[d]	10.9 (19)	7.8 (8)	11.8 (2)	0 (0)
Any eating disorder	10.3 (18)	5.9 (6)	23.5 (4)	25.0 (2)
Any Axis II	40.2 (70)	52.0 (53)	58.8 (10)	75.0 (6)
Multiple comorbid disorders[e]	44.3 (77)	24.5 (25)	41.2 (7)	25.0 (2)

[a]Values expressed as % (N) except where otherwise noted.
[b]Original categories defined by Statistics Finland; data missing on 12 outpatients.
[c]At T2, N = 102 for the clinic group (including subjects with a depressive disorder diagnosis at T2) and N = 8 for the school control group.
[d]Includes oppositional defiant disorder, attention-deficit/hyperactivity disorder, and conduct disorder.
[e]At least 2 other comorbid Axis I diagnoses in addition to the depressive disorder.
Abbreviation: MDD = major depressive disorder.
Symbol: … = no change.

In all, 50.0% (N = 87) of the outpatients experienced recovery at some point between T1 and T2, but 22 subjects (12.6%) had at least 1 recurrent depressive episode after the index episode. Median time to recurrence was 10.9 weeks (IQR, 4.43–17.4 weeks). Total median episode duration of the index episode among those who recovered (N = 87) was 58.9 weeks (IQR, 39.1–91.3 weeks) and was dependent on the diagnostic category being highest in double depression (600 weeks) and dysthymic disorder (169 weeks), followed by first episode MDD (60.7 weeks), recurrent MDD (56.7 weeks), and minor depression (30.8 weeks) (Kruskal-Wallis, χ^2 = 31.1, p < .001). Median time from baseline to recovery was 30.0 weeks (IQR, 19.5–42.6) and also varied by the diagnostic category at presentation (Kruskal-Wallis, χ^2 = 15.6, p = .004): minor depression, 14.0 weeks; dysthymic disorder, 23.9 weeks; recurrent MDD, 30.1 weeks; first episode MDD, 30.9 weeks; and double depression, 42.7 weeks.

Among those with depression at T2, psychiatric Axis I and Axis II comorbidity continued to be common (Table 1). Of subjects recovered from depression by T2, 30.6% (N = 22) continued to have other nonaffective Axis I psychiatric disorders, most commonly anxiety disorders (13.9%, N = 10). Axis II disorders were identified in 11 nondepressed adolescent outpatients (15.3%) at T2.

Course of Depression: School Controls

The distribution of depressive disorder diagnoses in the school controls at study entry was roughly similar to that in the clinic group, although unipolar MDD tended to be less frequent and minor depression more frequent in the controls (χ^2 = 8.04, df = 4, p = .09) (Table 1). Approximately half (52.9%; N = 9) of the controls with any unipolar depressive disorder at T1 had recovered by T2 (Table 1), a comparable rate to the clinic group (OR = 1.79, 95% CI = 0.63 to 5.06). If full remission of MDD were defined as recovery, the rate would have been 58.8% (N = 10) (Table 1). One subject (5.9%) had newly diagnosed bipolar disorder at T2.

Total median index episode duration among the school controls who recovered (N = 11) was 58.6 weeks (IQR, 15.1–123 weeks), which was comparable with the clinic group (Mann-Whitney U, z = –0.63, p = .53). Median

time from study entry to recovery was shorter in controls (9.0 weeks; IQR, 1.5–16.3 weeks; Mann-Whitney U, z = –2.92, p = .003). In all, 11 adolescents (64.7%) in the control group recovered from the index episode, with 5 subjects (29.4%) having a recurrence during the follow-up. The median time to recurrence was 19.3 weeks (IQR, 13.1–32.3 weeks). Controls seemed to have a higher recurrence rate (OR = 2.88, 95% CI = 0.96 to 8.96), but they reported longer median time to recurrence (Mann-Whitney U, z = –1.81, p = .08) than the outpatients.

Comorbidity was commonly identified in depressed controls at T2 (Table 1). Nonaffective Axis I and Axis II disorders continued in 2 (22.2%) and 1 (11.1%) of the recovered subjects, respectively.

Predictors of Depression Status at T2 (clinic group only)

Univariate analyses on the characteristics at T1 predicting the status of depression at T2 are presented in Table 2. The diagnoses of recurrent MDD and double depression, GAF total sum score and GAF score of 60 or lower at T1, and multiple current comorbid Axis I diagnoses at T1 were associated with persistent depression versus recovery at T2. Factors associating with recurrent depression versus recovery at T2 included older lifetime age of onset of depression and any Axis II comorbidity at T1.

In multivariable logistic regression analyses including all the variables significant in univariate analyses and adjusted for age and sex, none of the variables remained statistically significant in predicting persistent depression in the 1-year follow-up, although recurrent MDD (OR = 4.27, 95% CI = 0.90 to 20.3) and GAF score of 60 or lower approached significance (OR = 2.20, 95% CI = 0.90 to 5.31). Both older lifetime age at onset of depression (OR = 1.34, 95% CI = 1.02 to 1.76) and any Axis II comorbidity (OR = 3.35, 95% CI = 1.16 to 9.65) at T1 predicted recurrent depression at T2. No significant interactions between independent variables were observed in these analyses.

Predictors of Time to Recovery and Time to Recurrence (clinic group only)

In univariate survival analysis, longer time to recovery was predicted by older age at presentation, longer episode duration by study entry, depressive disorder diagnostic category, younger lifetime age at onset and childhood (< 12 years) age at onset, multiple comorbid Axis I diagnoses, and lower GAF score and GAF score of 60 or lower at T1 (Table 2). With the exception of multiple comorbid Axis I diagnoses and age at study entry, the predictors identified in the univariate analyses retained their significance in the multivariate Cox regression model (Table 3). Moreover, a significant interaction (p = .04) between episode duration by T1 and each depressive disorder diagnosis (with minor depression as the reference category) was identified, indicating that the effect of the diagnostic category needs to be evaluated in the context of illness duration.

Shorter time to recurrence was associated with older lifetime and adolescent (≥ 12 years) lifetime age at onset, any Axis II comorbidity, and shorter episode duration by T1 in univariate analyses (Table 2). In multivariate modeling, any Axis II comorbidity and shorter total index episode duration by T1 were significant predictors of shorter time to recurrence (Table 4).

DISCUSSION

Approximately 50% of the depressive episodes persisted beyond the 1-year follow-up time, and 40% of the initially depressed outpatients were in recovery at the 1-year follow-up interview. The diagnostic category of depression in the context of illness duration by study entry was a significant predictor of course and outcome of depression, and persistent and recurrent forms of depression were identified. We conclude that depressive episodes often persist many years, and even apparently milder forms of depression, i.e., minor depression, take many months on average to resolve. Prognosis, in terms of recovery rate and time to recovery, was comparable between the clinic group and school controls, further underlining the fact that adolescent depressive disorders carry a high burden of disease whether identified in treatment settings or in the general population. In our study, factors predicting the outcome were lifetime age at onset of depression and age and psychosocial functioning at presentation. The impact of comorbidity was noted in any Axis II comorbidity being a significant predictor of shorter time to recurrence in multivariate analysis, but the characteristics of depression were generally better predictors of the outcome than psychiatric comorbidity.

Course and Outcome of Depression

In general, outcome definitions tend to vary between studies, and consistent definitions enabling comparisons across databases have been called for.[1,2,15] In naturalistic, clinical longitudinal studies on MDD in which full remission or recovery is required to reach outcome, the recovery rates vary greatly between 40% and 90%,[1,2,4,6–8,15,20] at least partially depending on methodological variation (e.g., length of follow-up, age distribution of study population, proportion of subjects receiving treatment, proportion of subjects with first episode depression, interview instrument, and informants used). Recovery rates are generally at the lower end of the range in studies comprising consecutively referred patients or otherwise unselected samples including subjects with severe and/or highly comorbid depression. Our estimates of median episode duration were at the higher end of the range of previous

Table 2. Univariate Analyses on Predictors of Unipolar Depressive Disorder Outcome, Time to Recovery, and Time to Recurrence at 12 Months (T2) Among Adolescent Psychiatric Outpatients (N = 174)[a]

Characteristic at Baseline (T1)	Predictors of Depression Outcome at T2					Predictors of Time to Recovery (N = 174), HR (95% CI)	Predictors of Time to Recurrence (N = 174), HR (95% CI)
	A: Recovered at T2 and No Recurrences During the Study Period (N = 66)	B: Persistent Depression at T2 (N = 86)	C: Recurrence Between T1 and T2 (N = 22)	B vs A, OR (95% CI)	C vs A, OR (95% CI)		
Sociodemographics							
Sex, female	81.8 (54)	79.1 (68)	86.4 (19)	0.84 (0.37 to 1.89)	1.41 (3.56 to 5.53)	1.22 (0.69 to 2.17)	1.71 (0.51 to 5.77)
Age, median (IQR), y	16.0 (15.0–18.0)	17.0 (15.0–18.0)	17.0 (15.8–17.0)	1.11 (0.91 to 1.34)	1.09 (0.79 to 1.50)	0.88 (0.77 to 1.00)	1.02 (0.79 to 1.32)
Characteristics of depression (continuous variables), median (IQR)							
Episode duration by T1, wk	26.6 (9.8–61.3)	34.4 (14.7–101)	21.3 (11.5–26.7)	1.00 (0.999 to 1.00)	0.99 (0.99 to 1.00)	0.97 (0.96 to 0.98)	0.99 (0.97 to 1.00)
Lifetime age at onset, y	13.5 (12.0–16.0)	13.0 (11.0–14.3)	15.0 (13.0–16.3)	0.94 (0.84 to 1.06)	1.30 (1.03 to 1.63)	1.27 (1.16 to 1.40)	1.31 (1.10 to 1.57)
BDI-21 total sum score	19.0 (14.0–28.0)	21.5 (16.0–28.0)	22.0 (15.0–32.5)	1.02 (0.98 to 1.05)	1.02 (0.97 to 1.07)	0.98 (0.96 to 1.01)	1.01 (0.97 to 1.06)
HAM-D-17 total sum score	14.5 (11.0–20.0)	15.0 (11.0–20.0)	12.0 (8.0–18.0)	1.02 (0.97 to 1.07)	0.94 (0.88 to 1.02)	0.99 (0.96 to 1.03)	0.94 (0.87 to 1.01)
GAF score	55.0 (45.0–61.0)	50.0 (45.0–55.0)	50.0 (45.0–60.3)	0.96 (0.93 to 0.996)	1.00 (0.96 to 1.05)	1.04 (1.02 to 1.06)	1.02 (0.98 to 1.06)
Characteristics of depression (categorical variables)							
Lifetime age at onset < 12 years	21.2 (14)	34.9 (30)	4.5 (1)	1.95 (0.93 to 4.09)	5.77 (0.71 to 1.47)	0.30 (0.16 to 0.56)	0.13 (0.02 to 0.96)
GAF score ≤ 60	72.7 (48)	88.4 (76)	77.3 (17)	2.85 (1.21 to 6.69)	1.28 (0.41 to 3.40)	0.36 (0.22 to 0.59)	0.86 (0.32 to 2.33)
Diagnostic category							
First MDD	53.0 (35)	50.0 (43)	54.5 (12)	3.28 (0.81 to 13.3)	0.55 (0.15 to 2.00)	0.23 (0.12 to 0.45)	3.16 (0.92 to 10.9)
Recurrent MDD	21.2 (14)	30.2 (26)	22.7 (5)	4.95 (1.13 to 21.7)	0.57 (0.13 to 2.60)	0.22 (0.11 to 0.46)	1.23 (0.43 to 3.49)
Dysthymic disorder	9.1 (6)	5.8 (5)	0	2.22 (0.38 to 13.1)	…[b]	0.11 (0.04 to 0.31)	…[b]
Double depression[c]	4.5 (3)	10.5 (9)	0	8.00 (1.24 to 51.5)	…[b]	0.02 (0.01 to 0.11)	…[b]
Minor depression	12.1 (8)	3.5 (3)	22.7 (5)	1.00	1.00	1.00	1.00
Comorbidity							
Any psychiatric comorbidity	74.2 (49)	79.1 (68)	95.5 (21)	1.31 (0.61 to 2.80)	7.29 (0.91 to 58.3)	0.80 (0.47 to 1.36)	5.90 (0.79 to 43.8)
Any Axis I diagnosis	69.7 (46)	76.7 (66)	77.3 (17)	1.44 (0.70 to 2.96)	0.68 (0.22 to 2.09)	0.62 (0.39 to 1.01)	1.20 (0.44 to 3.25)
Any Axis II diagnosis	31.8 (21)	41.9 (36)	59.1 (13)	1.47 (0.75 to 2.90)	3.10 (1.14 to 8.37)	0.71 (0.46 to 1.10)	2.38 (1.02 to 5.56)
Multiple comorbid Axis I diagnoses[d]	34.8 (23)	51.2 (44)	45.5 (10)	1.96 (1.01 to 3.79)	1.56 (0.59 to 4.15)	0.49 (0.31 to 0.77)	1.02 (0.44 to 2.36)
Any anxiety disorder	54.5 (36)	58.1 (50)	63.6 (14)	1.16 (0.67 to 2.21)	1.46 (0.54 to 3.94)	0.71 (0.46 to 1.10)	1.37 (0.57 to 3.26)
Any substance use disorder	15.2 (10)	18.6 (16)	13.6 (3)	1.28 (0.54 to 3.04)	0.88 (0.22 to 3.55)	0.99 (0.55 to 1.80)	0.79 (0.23 to 2.66)
Any disruptive disorder[e]	6.1 (4)	15.1 (13)	9.1 (2)	2.76 (0.86 to 8.90)	1.55 (0.26 to 9.12)	0.54 (0.22 to 1.33)	0.72 (0.17 to 3.10)
Any eating disorder	6.1 (4)	12.8 (11)	13.6 (3)	2.27 (0.69 to 7.49)	2.45 (0.50 to 11.9)	0.70 (0.32 to 1.51)	1.31 (0.39 to 4.41)

[a]Values expressed as % (N) unless otherwise noted.
[b]Excluded from the analyses due to zero cells in 2 categories.
[c]Dysthymic disorder with a superimposed episode of MDD.
[d]At least 2 other comorbid Axis I diagnoses in addition to the depressive disorder.
[e]Includes oppositional defiant disorder, attention-deficit/hyperactivity disorder, and conduct disorder.
Abbreviations: BDI-21 = 21-item Beck Depression Inventory, GAF = Global Assessment of Functioning, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, HR = hazard ratio, IQR = interquartile range, MDD = major depressive disorder, OR = odds ratio.

Table 3. Cox Regression Analysis on Time to Recovery Among Adolescent Psychiatric Outpatients With Unipolar Depression at Baseline (T1) (N = 174)

Characteristic at Baseline (T1)	Wald	p Value	HR (95% CI)
Sex: male	…	…	1.00
Sex: female	0.25	.62	0.86 (0.46 to 1.59)
Age	1.68	.20	0.90 (0.78 to 1.05)
Lifetime age at onset for depression <12 years: no	…	…	1.00
Lifetime age at onset for depression <12 years: yes	5.36	.02	0.42 (0.20 to 0.88)
GAF total sum score	8.96	.003	0.45 (0.26 to 0.76)
Diagnostic category	15.1	.005	
Minor depression (reference)	…	…	1.00
First MDD	9.53	.002	0.13 (0.04 to 0.47)
Recurrent MDD	11.7	.001	0.09 (0.02 to 0.36)
Dysthymic disorder	3.37	.07	0.12 (0.01 to 1.16)
Double depression[a]	4.57	.03	0.00 (0.00 to 0.38)
Multiple Axis I comorbid diagnoses[b]: no	…	…	1.00
Multiple Axis I comorbid diagnoses[b]: yes	2.70	.10	0.66 (0.40 to 1.08)
Index episode duration by study entry	10.2	.001	0.88 (0.81 to 0.95)

[a]Dysthymic disorder with a superimposed episode of MDD.
[b]At least 2 other comorbid Axis I diagnoses in addition to the depressive disorder.
Abbreviations: GAF = Global Assessment of Functioning, HR = hazard ratio, MDD = major depressive disorder.
Symbol: … = reference category.

Table 4. Cox Regression Analysis on Time to Recurrence Among Adolescent Psychiatric Outpatients With Unipolar Depression at Baseline (T1) (N = 174)

Characteristic at Baseline (T1)	Wald	p Value	HR (95% CI)
Sex: male	…	…	1.00
Sex: female	1.42	.23	2.12 (0.63 to 7.30)
Age	0.03	.86	1.02 (0.78 to 1.34)
Lifetime age at onset of depression < 12 years: no	…	…	1.00
Lifetime age at onset of depression < 12 years: yes	2.15	.14	0.22 (0.03 to 1.67)
Any Axis II comorbidity: no	…	…	1.00
Any Axis II comorbidity: yes	5.49	.02	2.90 (1.19 to 7.06)
Index episode duration by study entry	3.54	.02	0.99 (0.97 to 1.00)

Abbreviation: HR = hazard ratio.

reports on mean duration,[4,6–8] but are in line with findings by, for example, Dunn and Goodyer[3] and Birmaher et al.[20]

The recovery rate of depression was similar in the school controls and clinically referred adolescents. It should be noted that although the controls initially had lower BDI-21 scores and significantly lower rates of childhood-onset depression, they were equally impaired in comparison to the outpatients.[9] Moreover, the proportion of minor depression was somewhat higher and the proportion of MDD lower among the controls than the outpatients, although the differences were not statistically significant and approximately half of the controls reported contacting adolescent psychiatric services by T2. These findings are in line with earlier studies suggesting that clinical samples are biased toward more severely depressed adolescents.[21,22] Lewinsohn et al.[21] linked treatment seeking with longer time to recovery, which was interpreted to be the consequence of more severely depressed youths referring to treatment. Angold et al.[22] have suggested that adolescents seeking psychiatric treatment are on a different trajectory from those not using services, i.e., treatment-seeking youths have a trend of deterioration, which can be halted or reversed during treatment, while those not entering treatment at all tend to get better anyway as time passes. This accords with findings of shorter time from baseline to recovery in controls compared to the clinic group. Thus, it may well be that the benefit of treatment is seen in patients (with more severe depression and possibly deteriorating course) reaching roughly similar outcome to the controls (with less severe depression and possibly recovering, "natural" course), although this remains for further studies to be investigated.

High risk of recurrence of depressive episodes in young people has been a consistent finding across studies.[7,15,23,24] In our sample, the recurrence rate in the clinic group was relatively low, probably due to the limited follow-up time, stringent recovery criteria, and subsequently low proportion of subjects with the possibility of a new episode.[15] The proportionately large subgroup of subjects with partial remission raises concerns about residual symptoms, which are likely to be impairing and increase the risk of relapse.[25] A subgroup of adolescents who recovered from depression continued to have other nonaffective psychiatric disorders, indicating that they were still at an increased risk of further depressive episodes. Controls appeared to have longer time to recurrence, albeit a slightly higher recurrence rate, which may again serve as a marker for lower severity of depression on a group level.

Predictors of Outcome, Time to Recovery, and Time to Recurrence: Characteristics of the Depressive Episode and Sociodemographics

Longer episode prior to entering treatment predicted slow recovery, which accords with earlier data.[26] Subjects with chronic forms of depression according to diagnostic definition (dysthymic disorder and double depression) eventually recovered almost as often as youths with episodic depression (MDD and minor depression) within the limited 1-year follow-up time, although median time from baseline to recovery was longer in those with chronic depression. The interaction between episode duration and diagnostic category suggests that illness duration, also part of the diagnostic criteria, is a strong predictor of course and outcome. It should be further noted that especially adolescents with dysthymic disorder or double depression already had episodes of many years' duration prior to entering treatment, implying a significant delay in treatment

referral compared to other diagnostic groups. On the other hand, an initially short episode duration was associated with shorter time to recurrence, a finding both supported[21] and contradicted[7] by earlier literature.

Studies distinguishing between chronic and episodic forms of depression suggest that these 2 categories are actually separate entities with, for example, different course and predictors of outcome[27] and with differing patterns of comorbidity.[10] This issue has been little studied in clinically referred adolescents, but earlier data are in line with our findings and suggest that especially double depression in adolescence is a strong predictor of prolonged depression.[1,3,6] On the other hand, recurrent depressive episodes could be viewed as chronic illness, as recurrence predicts worse long-term prognosis and a higher risk of future episodes than a single episode in adolescence.[20,28] In our study, recurrent MDD at baseline was also associated with the status of persistent depression at T2, although this result fell below statistical significance in multivariate analysis.

Severity of depression as measured by either adolescent-rated (BDI-21) or researcher-rated (HAM-D-17) symptom scales was not related to course or outcome of depression. Impairment and the diagnosis of depression appeared to be more accurate predictors of outcome than symptom-load. Previous studies have shown that poor psychosocial functioning at presentation associates with lower likelihood of response.[5,8]

The analyses on time to recovery revealed that younger lifetime and childhood (< 12 years) age at onset of depression associated with increased episode duration, while older lifetime age at onset predicted recurrent episodes. Early or childhood age at onset has been especially linked with chronic depression,[21,24,29] but there are also data suggesting that there are no differences in the course of child-onset and adolescent-onset depressions.[3,8,20] Previously, older age during the index episode—older adolescents being more likely to have had time for longer illness durations—has been linked with longer recovery time and higher likelihood of persistent depression.[4,8,20,24,26] In line with our data, it has been suggested that gender is not among the main predictors of outcome of depression,[2] although the female preponderance in our study sample may have precluded our ability to find sex differences.

Predictors of Outcome, Time to Recurrence, and Time to Recovery: Comorbidity

Axis I. We have previously reported that the presence of co-occurring psychiatric disorders indicates more severe and impairing depression.[9] Many authors report associations between specific comorbid disorders or comorbidity in general and poor outcome of depression in comparison with depression alone.[4,6,8,26] The findings are inconsistent, however.[15,20,24] Comorbidity as a dichotomized measure (yes vs. no) can be treated as a measure of overall severity of psychopathology, while analyses on the influence of specific disorder categories yield more specific information on the course and outcome of depression in different contexts of psychopathology. In our study, the presence of multiple comorbid Axis I disorders was applied as a measure of breadth of psychopathology and was associated with persistent depression in univariate analyses. Adjustment with psychosocial functioning and depressive disorder diagnosis caused the association to disappear, suggesting that the latter 2 were more accurate predictors of outcome in this regard.

When the impact of specific comorbid disorder categories was analyzed, we were unable to detect any specific predictive influence between the main Axis I diagnostic categories and the course and outcome of depression. Earlier data support the association of disruptive,[4,6,26,30] anxiety,[4,25,30] and substance use disorders (SUDs)[8] with worse prognosis of depression in comparison with depression alone. However, previous studies diverge on these issues, too: for example, Sanford et al.[8] and Birmaher et al.[20] found no association between anxiety disorders and the prognosis of depression, whereas a recent publication from the Treatment for Adolescents with Depression Study reports no specific associations between depression and any comorbidity other than anxiety disorders.[26] In the Finnish health care system, adolescents with the most severe or primary SUD and most severe eating disorder are referred to the social welfare system and to specialized units, respectively, which may have diluted our ability to detect the possible influences of SUD and eating disorder on depression outcome in our study population.

Axis II. The area of personality disorder has been little studied in adolescents, so far. In our study, the presence of Axis II disorders at baseline discriminated those with recurrent depression from those who recovered from depression by T2. An Axis II diagnosis also played a strong role when the predictors of time to recurrence were identified. In accordance with our data, prior research suggests that a comorbid personality disorder diagnosis in adolescence predicts longer episodes, higher likelihood of recurrence, and greater severity of depression later in adolescence and young adulthood.[28,31,32] In adults, the compromising effect of personality disorders on the course and treatment outcomes of depression appears evident.[33]

Adolescent psychiatric studies have not usually included assessment of personality traits because adolescent years are considered to be the time when personality is developing and its characteristics are, therefore, unstable. It seems, however, that although Axis II diagnoses may be unstable over time, especially in adolescent subjects and subjects with an ongoing depression, they can be recognized in adolescents and have some predictive significance in adolescent psychiatric disorders.[34–36] Thus, the inclusion of personality traits in the assessment of

young people should be further investigated as personality traits may have predictive value and could influence the selection of future treatment interventions.[33]

Methodological Considerations

Compared with prior naturalistic clinical research on adolescent depression, our study included a wider spectrum of mood disorders and accompanying disorders. Existing studies differ methodologically in many ways, making comparisons with the prior literature challenging. Our assessment of adolescents was comprehensive and based on well-established interview instruments and self-report scales in a sample of consecutively referred adolescents. The results are generalizable to adolescent psychiatric outpatient populations, although generalizations to other cultures should take into account possible differences between health care systems (e.g., mixed child-adolescent clinical populations vs. strictly adolescent-aged populations in Finland).

The screen may have been rather tight[9] and the screening procedure may have initially excluded some of the outpatients with milder depressions. The relatively large drop-out rate among the screening positives at baseline is a weakness of this study.[9] As the dropouts and those refusing to participate scored lower on the screening instruments, it is likely that the subjects selected for this study represent those with more severe depression than those lost to attrition. On the other hand, the attrition at 12-month interview was relatively low and was not biased in terms of psychopathology of depression, which strengthens the generalizability of the results. Despite the comparably large study population, the small cell size in some categories precluded some detailed analyses of interest, for example, on individual comorbid psychiatric diagnoses.

We chose to interview only the adolescents themselves, as depressive disorders were the primary focus of this project. Regarding depressive symptoms, there is a reportedly low agreement between different informants and no uniform method of combining data from multiple sources.[8,37] Adolescents can be considered as valid informants of their own depressive symptoms and other "internalizing" disorders, while the use of adolescent informants only may have provided us with lower bound estimates of "externalizing disorders" (e.g., conduct disorders and SUD). In this regard, lack of interview data from parents and teachers is a limitation.[37] Complementary data were, however, available from clinical records, which included data collected from family and school as part of regular clinical work, and these were used to collect relevant background data on, for example, school, family, and earlier medical history.[10] The age at onset data were obtained retrospectively, which can be considered as a limitation. Data on personality disorders need to be interpreted with caution.

The predictors of outcome, i.e., plausible targets for interventions, are likely to be more complex than presented here and to extend beyond the clinical phenotype. We did not include in this study, for example, psychosocial factors (e.g., the significance of family background or social support) or life events, biological variables, or the impact of treatment received, but these issues are worthy of further investigation. Moreover, a longer follow-up is needed.

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