ORIGINAL ARTICLE

Preschool Depression

Homotypic Continuity and Course Over 24 Months

Joan L. Luby, MD; Xuemei Si, MS, MPH; Andy C. Belden, PhD; Mini Tandon, DO; Ed Spitznagel, PhD

Context: Childhood depression is a serious and relapsing psychiatric disorder. However, to date studies have focused mostly on children aged 6 years and older. Validation for depression in preschool children has been provided by 2 independent study samples. While several studies have demonstrated stability and poor outcomes of internalizing symptoms in preschoolers, there has not yet been longitudinal data available to inform the course of preschool depression and whether it shows homotypic continuity into early childhood.

Objective: To examine the 24-month course of preschool depression and whether it showed homotypic vs heterotypic continuity or was a developmentally transient phenomenon.

Design: Blindly rated, prospective, 24-month, longitudinal follow-up study.

Setting: Community sites.

Patients: Three hundred six preschoolers aged 3 to 6 years recruited from community sites and oversampled for symptoms of depression.

Main Outcome Measure: Recurrence/stability of depression and predictors of course.

Results: Preschoolers with depression at baseline had the highest likelihood of subsequent depression 12 and/or 24 months later compared with preschoolers with no baseline disorder and with those who had other psychiatric disorders. Preschoolers with depression at baseline were more likely to have later depression rather than other psychiatric disorders. Findings from a logistic regression analysis indicated that when controlling for demographic variables, risk factors, and comorbid disorders, depression during the preschool period and family history of affective disorders were the most robust and significant predictors of later depression.

Conclusions: Preschool depression, similar to childhood depression, is not a developmentally transient syndrome but rather shows chronicity and/or recurrence. Homotypic continuity of preschool MDD during a 24-month period was found. These results underscore the clinical and public health importance of identification of depression as early as preschool. Further follow-up of preschoolers with depression is warranted to inform the longitudinal course throughout childhood.

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Author Affiliations:
Washington University School of Medicine in St Louis, St Louis, Missouri.

THE VALIDITY OF MAJOR DEpressive disorder (MDD) in childhood has been well established, with the disorder now widely recognized and treated in mental health settings.[1-4] Beginning with the seminal work of Kovacs et al,[5,6] over the past 2 decades empirical data have shown that MDD in school-aged children (aged 6-12 years) is a serious clinical condition characterized by a relapsing course and is not merely a developmentally transient phenomenon.[7,8] Longitudinal data from clinical samples of school-aged children with depression have demonstrated recurrence rates of 40% after 2 years and 70% after 5 years.[5,6,9] Genetic vulnerability for MDD, the experience of stressful life events, as well as the presence of comorbid psychiatric disorders during childhood have emerged as key risk factors for depression onset and recurrence at school age as well as later in life.[10-14]

To date, studies of childhood MDD have focused predominantly on children aged 6 years and older. However, more than 20 years ago, data began to emerge that suggested that depression conforming to the diagnostic criteria found in the *DSM-III-R* could be identified even earlier in life in preschool-aged children.[15-18] Contradicting traditional developmental theory,[19] which claimed that young children were too cognitively and emotionally immature to experience depressive affects, recent empirical studies using new and age-appropriate

methods have identified *DSM-IV* unipolar MDD in preschoolers.[20] To date, preschool MDD has been identified and described in the empirical literature in 4 large independent samples from 3 geographical sites.[21-24] One epidemiological study estimates the prevalence rate of preschool MDD at 2.1%, the same rate found in school-aged children.[23] In an investigation that screened preschoolers (N=175) from both clinical and community sites, *DSM-IV* MDD was identified using a structured age-appropriate psychiatric interview.[22] The typical symptoms and vegetative signs of depression emerged as sensitive and specific manifestations of the disorder in preschoolers rather than as masked symptoms, such as somatic complaints or aggression, which were previously expected to characterize depression in younger children.[25] However, in this investigation, a large group of preschoolers who met all *DSM-IV* symptom criteria and had high depression severity and impairment failed to meet the strict 2-week duration criterion.[26] This finding suggested that the strict duration criterion may not apply to such young children and should be "set aside" in preschool MDD.

Validation for preschool MDD (based on meeting all *DSM-IV* symptom criteria) has been supported by the finding of a specific symptom constellation that was distinct from other psychiatric disorders and stable during a 6-month period.[22] Additionally, alterations in the hypothalamic-pituitary-adrenal axis reactivity similar to those known in adults with depression, greater family history of mood disorders, as well as observational evidence of depressive affects and behaviors were detected in preschoolers with depression, providing further validation.[22,25,27-30] More recent findings from a larger independent sample (N=306) ascertained from community sites (and serving as the population for this investigation) have replicated the findings described above and have also demonstrated that preschoolers with depression display significant functional impairment evident in multiple contexts rated by both parents and teachers.[24]

Despite this growing body of empirical data validating preschool MDD, skepticism remains as to whether the preschool-onset form is clinically meaningful and/or specific or whether it is a transient developmental phenomenon or a nonspecific precursor of other later psychopathology. It also remains to be established whether preschool onset MDD, if not self-limited, is continuous with school-aged depression. Also unknown and of interest is whether preschool MDD has a remitting and relapsing course similar to school-aged MDD and, related to this, whether the same risk factors for recurrence or chronicity are operative. The purpose of this longitudinal study was to address these research questions.

It was hypothesized that preschool depression would show homotypic continuity over the course of 24 months, evidenced by a greater likelihood of subsequent depression when compared with rates observed in those with other psychiatric disorders and those without disorders at baseline. In addition, it was hypothesized that preschool depression would show greater homotypic rather than heterotypic continuity as evidenced by a greater likelihood of subsequent depression as opposed to other psychiatric outcomes. Furthermore, it was hypothesized that depression at baseline would predict later depression after controlling for comorbid psychiatric disorders and known risk factors. Preschool MDD was expected to have a remitting and relapsing course during 24 months. The current study also examined risk/protective factors that contribute to the course of preschool MDD. Based on the literature in older children, it was hypothesized that preschoolers with a greater family history of affective disorders, who experienced more stressful life events, or who had greater comorbidity would be at an increased risk for recurrent and more severe depressive episodes during a 24-month period.

To date, several studies have followed up preschoolers with internalizing symptoms or disorders and established stability as well as risk of poor later childhood outcomes.[31,32] Furthermore, associations between temperament during the preschool period and later risk of depression in early adulthood have been demonstrated.[33] However, to our knowledge this is the first available longitudinal follow-up data from a sample of 3- to 6-year-old children who met *DSM-IV* MDD symptom criteria to inform the continuity and course of preschool MDD.

METHODS

RECRUITMENT AND PARTICIPANTS

This investigation used data from a National Institute of Mental Health–funded Validation of Preschool Depression Study. The Preschool Depression Study is an ongoing, multi-method, multi-informant (parents, children, and teachers), longitudinal investigation of 306 preschoolers. Comprehensive assessments were conducted at 3 annual waves in the Early Emotional Development Program at the Washington University School of Medicine in St Louis, St Louis, Missouri. From May 2003 to March 2005, children aged 3 to 5.11 years were recruited from pediatricians' offices, daycare centers, and preschools in the St Louis metropolitan area using the Preschool Feelings Checklist (PFC).[34] Approximately 6000 PFCs were distributed to recruitment sites and 1474 PFCs (25%) were returned to the Early Emotional Development Program. Caregivers who endorsed no items on the PFC; 2 or more internalizing items; and/or 2 or more externalizing items (n=899) were contacted by telephone for further screening. Excluded were children with chronic medical illnesses, neurological problems, pervasive developmental disorders, or language and/or cognitive delays as well as those outside of the study age range. Of the 416 eligible caregiver-child dyads, 306 agreed to participate and presented for baseline assessment; details have been published previously.[24] It is important to note that the recruitment techniques used in this study were designed to oversample for preschoolers with or at risk of depression. Therefore, the recruitment numbers provided cannot be used to estimate the prevalence rates of preschool MDD in the general population.

MAIN MEASURES

Preschool Depression Screener

The PFC[34] is a 20-item parental report checklist designed to identify preschoolers (age 3.0-6.0 years) with symptoms of depression. Previous findings examining the sensitivity and specificity of the PFC suggest that it is a valid and reliable screener for identifying preschoolers with or at risk of mood and/or disruptive disorders.[35]

Diagnostic Assessment

The Preschool-Age Psychiatric Assessment (PAPA)[36] is an interviewer-based, caregiver-reported diagnostic assessment with established test-retest reliability designed for use with primary caregivers of children aged 2.0 to 6.0 years that has become widely used in preschool psychopathology research.[37] The PAPA includes all relevant *DSM-IV* criteria and their age-appropriate manifestations. Diagnoses are derived from computer algorithms that apply all of the *DSM-IV* criteria. For this investigation, the 2-week duration criterion for MDD was set aside; however, information about episode durations within the depressed group are provided below. The PAPA rates the intensity of symptoms, their frequency and duration, as well as impairment from symptoms.

As recommended by the authors of the measure, interviews were audiotaped for later quality control and interviewer calibration. Approximately 20% of tapes were reviewed by a master coder, and when discrepancies arose, they were recoded in consultation with a senior child psychiatrist (J.L.L.). In addition to coding checks, weekly coding meetings with a master rater were conducted to maintain calibration and avoid rater drift. These calibration techniques were deemed most appropriate to the structure of the interview by the authors of the measure rather than calculation of interrater reliability, as is the standard for semistructured interviews.

MDD Severity Score Calculations

In addition to categorical *DSM-IV* diagnoses, total MDD severity sum scores (ie, the total number of MDD symptoms endorsed in the PAPA) were computed. Previous findings have suggested that dimensional symptom sum scores are a sensitive measure of the severity of psychopathology.[28] The Pearson correlation coefficients among MDD severity scores across the 3 annual waves were 0.417 (baseline and 12 months), 0.450 (baseline and 24 months), and 0.508 (12 and 24 months) ($P<.001$ for all 3 correlation coefficients).

Experience of Stressful Life Events

Both stressful and traumatic life events were assessed using the PAPA. Examples of stressful life events assessed include parental separation or divorce, death of a pet, birth of a new sibling, and change in daycare or preschool. Examples of traumatic life events assessed include death of a parent, experience of physical or sexual abuse, and removal from one's home. The total number of stressful and traumatic life events prior to baseline were used in the analyses that follow. Costello et al[38] have established the test-retest reliability of parental reports of stressful and traumatic life events in the Child and Adolescent Psychiatric Assessment,[39] from which the PAPA was derived.

History of Family and Maternal Affective Disorders

The Family Interview for Genetic Studies[40] is a validated measure of family psychiatric history widely used in genetic research. It was administered to primary caregivers who provided psychiatric histories for first- and second-degree biological relatives. For the current study, family history of affective disorders represented the proportion of all first- and second-degree biological relatives (excluding mothers) reported to have had 1 or more affective disorders. In the analyses that follow, the maternal affective disorders variable was used as a dichotomous variable that represents whether a subject's mother ever had an affective disorder (yes or no). The Family Interview for Genetic Studies is a fully structured measure, and the senior investigator trained interviewers on its administration to reliability.[40] Any questions about the diagnostic status of a family member were reviewed by a senior psychiatrist blind to the proband (preschool subject) diagnosis. The Family Interview for Genetic Studies data were obtained on all subjects and updated at each study wave. However, for the analyses that follow, only incidences of affective disorders among family members that occurred prior to baseline were counted. Only 11 of 306 subjects (3%) had missing Family Interview for Genetic Studies data at baseline.

ASSESSMENT AND FOLLOW-UP

Caregiver-child dyads who completed the PFC and who met all inclusion/exclusion criteria came to the Early Emotional Development Program for a comprehensive 3- to 4-hour laboratory assessment at baseline. While children completed measures of emotional, cognitive, and social development, their primary caregivers (92% biological mothers, 3% biological fathers, and 5% adoptive/foster parents or grandparents) were interviewed separately about their preschoolers' psychiatric symptoms using the PAPA and about their developmental skills and impairments using a variety of other measures. At follow-up, assessments using identical diagnostic interviews (PAPA) as well as similar developmental and behavioral assessments were repeated with parents and children at 12 (wave 2) and 24 (wave 3) months following the baseline assessment (wave 1).

In addition to collection of diagnostic data on the entire sample at 3 annual waves, MDD modules of the PAPA were administered by telephone in a subset (157 eligible subjects) of depressed or prodromal preschoolers (defined by $\geq$4 symptoms of MDD and/or the symptom of anhedonia). Complete data were obtained in 119 preschoolers at 6 months and 119 preschoolers at 18 months following the baseline assessment. These interval assessments were done to obtain data on the continuous course of MDD and thus were of interest only for subjects with high levels of depressive symptoms. For the analyses on course, it is important to note that the PAPA does not specifically assess episode onsets and offsets. Therefore, for participants who met criteria for MDD on the PAPA, at each assessment we can only infer that they were experiencing an episode at some point during that 6-month period. For this investigation, the MDD module of the PAPA captured symptoms during the last 6 months. Therefore, the term *recurrence* was used when a subject experienced an episode within a 6-month period, had no episodes for a subsequent 6-month period, and experienced an episode after that. The term *chronic* was used when a subject experienced episodes in 4 or more assessment periods.

The primary caregiver informant remained the same in 96% of subjects across all study waves. Interviewers remained blind to preschoolers' diagnostic statuses throughout the entire study. Psychiatric diagnoses were derived by computer algorithms obtained from the authors of the PAPA at Duke University, using *DSM-IV* criteria (a procedure that made keeping interviewers unaware of participants' diagnostic status highly feasible). It is important to note that standard diagnostic algorithms were used for all diagnoses with the sole exception that the duration criteria for MDD were "set aside" as outlined previously. Descriptive data on episode duration within the MDD group are provided below.

STATISTICAL ANALYSIS

Differences Between Diagnostic Groups at Baseline

Cross tabulation (χ^2 tests) and analyses of variance (ANOVA) were used to examine demographic and risk factor differences between diagnostic groups at baseline. In addition, cross tabulation (χ^2 tests) and Mann-Whitney *U* tests were conducted as appropriate to examine differences in the same factors between preschoolers who attended later study waves and those who dropped out.

Table 1. Characteristics of the Sample at Baseline

Characteristic	Patients, No. (%)			χ^2	*P* Value
	MDD (n=75)	Psychiatric Disorder (n=79)	No Disorder (n=146)		
Age, y					
3	17 (23)	29 (38)	47 (32)	11.75	.02
4	27 (36)	34 (43)	66 (45)		
5	31 (41)	16 (20)	33 (23)		
Ethnicity					
White	38 (51)	39 (49)	87 (60)	4.38	.36
African American	26 (35)	27 (34)	45 (31)		
Other	11 (14)	13 (17)	13 (9)		
Sex					
M	45 (60)	40 (51)	70 (48)	2.93	.23
F	30 (40)	39 (49)	76 (52)		
Total family income, $					
≤20 000	19 (28)	19 (25)	25 (18)	7.83	.25
20 001-40 000	17 (25)	14 (19)	20 (15)		
40 001-60 000	12 (17)	12 (16)	27 (20)		
≥60 001	21 (30)	30 (40)	63 (47)		
Parental education					
High school diploma	16 (21)	14 (18)	27 (18)	12.19	.06
Some college	36 (48)	34 (43)	42 (29)		
4-year college degree	11 (15)	14 (18)	35 (24)		
≥Graduate education	12 (16)	17 (21)	42 (29)		
Parent marital status					
Married	32 (44)	43 (62)	94 (66)	12.37	.14
Widowed	0	0	1 (1)		
Separated	3 (4)	2 (3)	2 (1)		
Divorced	8 (11)	7 (9)	7 (5)		
Never married	30 (41)	27 (34)	39 (27)		
Maternal history of affective disorder	37 (50)	34 (44)	37 (26)	14.77	.001
No. of life events, mean (SD)					
Stressful life events	3.73 (2.09)	3.59 (1.88)	3.19 (1.91)	*F*=2.32	.10
Traumatic life events	1.75 (1.35)	1.54 (1.24)	1.24 (1.14)	*F*=4.56	.01
Total	5.48 (2.97)	5.14 (2.44)	4.43 (2.49)	*F*=4.57	.01
Age, mean (SD), mo	56.15 (9.95)	51.25 (9.49)	52.12 (9.15)	*F*=6.13	.002
MDD severity score, mean (SD)	8.83 (3.59)	3.86 (1.89)	1.75 (1.65)	*F*=226.66	<.001
Proportion of family history of affective disorder, mean (SD)	0.11 (0.13)	0.09 (0.10)	0.09 (0.12)	*F*=0.71	.49

Abbreviation: MDD, major depressive disorder.

Likelihood of Chronicity of Preschool MDD

Multinomial logistic regression analyses were conducted to test the likelihood that preschoolers in the MDD group vs those in the no-disorder or psychiatric comparison groups at baseline would have MDD, no disorders, or a psychiatric disorder at follow-up. Next, a logistic regression was conducted to test whether MDD diagnosis at baseline predicted MDD diagnosis at follow-up (12 and/or 24 months after baseline) while statistically controlling for demographic variables, comorbid diagnoses (split into separate disruptive and anxiety categories), stressful life events, and maternal and family history of affective disorders at baseline.

MDD Course During 24-Month Study Period

A repeated-measures univariate ANOVA was conducted to compare MDD severity scores among 3 depressed groups with different courses (recovered, recovered/recurred, and chronic). The 3 groups were defined using data from 5 assessment points that provided continuous information (MDD module assessed the last 6 months and assessment done every 6 months) about whether preschoolers were or were not in an episode during the 24-month study period. The MDD severity scores among previously depressed preschoolers at recovery were also compared with those of preschoolers in both the psychiatric control and no-disorder groups using nonparametric tests (Kruskal-Wallis and Mann-Whitney *U* tests).

MDD Chronicity/Recurrence in Preschool-Aged Children

Multinomial logistic regressions were conducted to examine whether specific risk factors were associated with the chronicity or recurrence of preschool MDD. The SPSS software, version 15.0 (SPSS Inc, Chicago, Illinois), was used to conduct all statistical analyses.

RESULTS

DIAGNOSTIC GROUPS AND SAMPLE CHARACTERISTICS

Using baseline diagnoses, preschoolers were categorized into 1 of 3 hierarchical diagnostic groups: (1) the MDD group was composed of those who met criteria for MDD and had any other comorbidity (n=75), (2) the psychiat-

ric group was composed of those who met criteria for any anxiety and/or disruptive disorders but did not have MDD (n=79) (anxiety disorders included separation anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. Disruptive disorders included attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder); (3) preschoolers were included in a no-disorder group (n=146) if they did not meet criteria for any psychiatric disorder. However, it is important to note that based on screening techniques used, those in this group may have had symptoms or prodromes of depression or other disorders. Two preschoolers met symptom criteria for bipolar disorder type I only at baseline and 4 preschoolers had excessive missing data; therefore, these 6 subjects were excluded from the analyses that follow.

Although the 2-week–duration criterion was set aside in the diagnostic algorithm for depression as described, 23% of subjects in the baseline MDD group met the 2-week duration criterion. Fifteen percent of subjects reported symptoms for more than 2 hours a day, 4 or more days a week but not for 2 consecutive weeks. Twenty-eight percent of subjects had symptoms for more than 2 hours a day but for fewer than 4 days in any given week, and 20% reported symptoms for less than 2 hours in any given day. Episode duration data were missing in 15% of subjects. Additional details about duration and frequency of depressive symptoms will be presented in a separate communication.

Results from a 1-way ANOVA with post hoc pairwise comparisons indicated that at baseline, preschoolers' age (in months) ($F_{2,297}=6.13$, $P=.002$) and number of traumatic life events experienced prior to baseline ($F_{2,296}=4.56$, $P=.01$) were significantly different among diagnostic comparison groups. Specifically, preschoolers in the depressed group were significantly older (mean age, 56.15 months [standard deviation (SD), 9.95 months]) than those in the psychiatric (mean age, 51.25 months [SD, 9.49 months], $P=.006$) and no-disorder (mean age, 52.12 months [SD, 9.15 months], $P=.01$) groups (**Table 1**). Preschoolers in the depressed group had experienced significantly more traumatic life events (mean, 1.75 [SD, 1.35]) than preschoolers in the no-disorder group (mean, 1.24 [SD, 1.14], $P=.02$). χ^2 Test results indicated that caregivers of preschoolers in the no-disorder group had a higher education level than caregivers in the MDD group ($\chi^2_3=10.77$, $P=.01$). There were significantly more maternal affective disorders among preschoolers in the depressed ($\chi^2_1=12.88$, $P<.001$) and psychiatric ($\chi^2_1=7.45$, $P=.006$) groups than in the no-disorder group. No other significant demographic or risk factor differences were found between diagnostic groups at baseline.

Two hundred fifty-six subjects (63 with MDD, 69 with psychiatric disorders, and 124 with no disorders) were retained during the longitudinal study. The Mann-Whitney U test and cross tabulations (χ^2 tests) were used to compare demographic and risk factor differences between those who remained and those who dropped out in each group. Within the no-disorder group, preschoolers who were white, had parents who were married, had higher family income and parental education levels, had a higher proportion of family members with a history of affective disorders, and had fewer stressful life events were less likely to drop out ($P<.05$ for all). The only significant difference found in the psychiatric group was that older preschoolers were more likely to be retained in the study ($P=.03$). No other statistically significant differences were found.

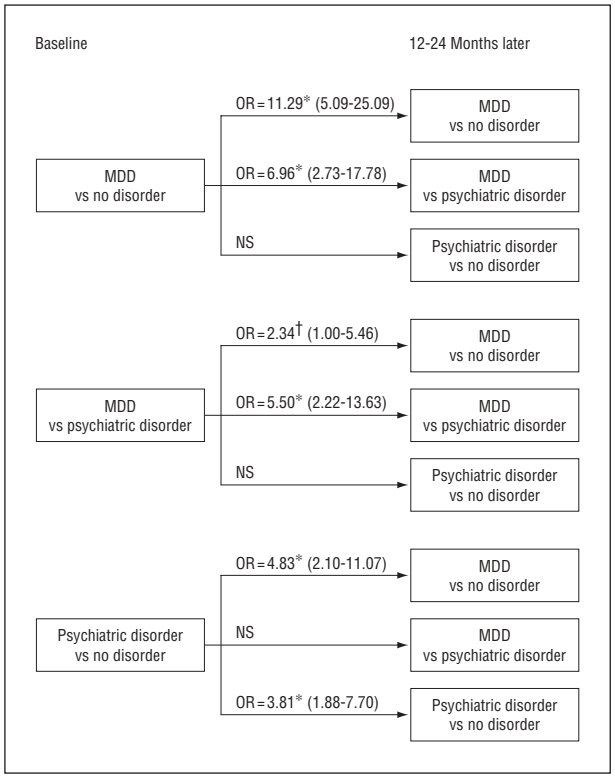

Figure 1. Homotypic vs heterotypic continuity of preschool depression and other psychiatric disorders. Odds ratios (ORs) are shown with 95% confidence intervals. MDD indicates major depressive disorder; NS, nonsignificant; *$P<.001$; †$P<.05$.

LIKELIHOOD OF LATER MDD

Results from multinomial logistic regressions are illustrated in **Figure 1**. Findings indicated that preschoolers with MDD at baseline were 11.3 times as likely as children with no disorders to be depressed instead of healthy at follow-up. Preschoolers with MDD at baseline were 7 times as likely as those with no disorder to have depression vs another psychiatric disorder at follow-up. Preschoolers with MDD at baseline compared with those with other psychiatric disorders were 2.3 and 5.5 times as likely, respectively, to be depressed instead of healthy and instead of having other psychiatric disorders at follow-up. (Figure 1 shows odds ratios [ORs] along with their 95% confidence intervals [CIs] for all comparisons).

MDD RECURRENCE ACCOUNTING FOR DEMOGRAPHICS, COMORBIDITIES, AND OTHER RISK/PROTECTIVE FACTORS

A simultaneous logistic regression model was significant (Cox and Snell $R^2=0.27$, $\chi^2_{14}=70.91$, $P<.001$) (**Table 2**). Demographic variables, comorbid disorders and other risk factors, and MDD at baseline were entered simultaneously. The diagnosis of preschool MDD

Table 2. Logistic Regression of Preschool MDD and Subsequent MDD Controlling for Key Risk Factors[a]

Variables Entered Into Model[b]	%	Wald χ^2	OR (95% CI)	*P* Value
Child's age, mean (SD), mo	53.12 (9.50)	2.84	1.03 (0.99-1.08)	.09
Sex (M=1/F=0), male	50	0.57	1.32 (0.65-2.68)	.45
Family income, $				
≤20 000	19.6	4.82	1 [Reference]	.19
20 001-40 000	17.4	0.93	0.56 (0.17-1.82)	.34
40 001-60 000	19.6	4.64	0.26 (0.07-0.89)	.03
≥60 001	43.5	2.47	0.37 (0.11-1.28)	.12
Maternal education				
High school	15.2	2.45	1 [Reference]	.48
Some college education	36.1	0.92	1.79 (0.54-5.90)	.34
4-year college degree	22.2	0.41	1.61 (0.37-7.01)	.52
≥Graduate education	26.5	0.02	0.89 (0.20-4.06)	.88
Disruptive disorder	33.0	7.44	3.04 (1.37-6.77)	.006
Anxiety disorder	22.6	1.17	1.56 (0.70-3.49)	.28
No. of stressful life events, mean (SD)	4.75 (2.62)	1.18	1.09 (0.94-1.26)	.28
Maternal history of affective disorder	37.4	0.12	0.87 (0.40-1.92)	.73
Family history of affective disorder, mean (SD), %[c]	10.17 (12.06)	14.70	1.07 (1.03-1.10)	<.001
Preschool MDD	24.3	10.78	3.64 (1.68-7.88)	.001

Abbreviations: CI, confidence interval; MDD, major depressive disorder; OR, odds ratio.
[a] This model included a total of 230 subjects with valid data for all 10 variables. Model $\chi^2_{14}=70.91$, $P<.001$.
[b] All variables were recorded at baseline, except for stressful life events, which were the total events the child had encountered both prior to baseline and during study periods.
[c] The usual range of family history of affective disorder is 0% to 60%; the OR of later MDD increases by a factor of 2.6 for those who had 14% of relatives with affective disorders (the third quartile) compared with those who had no relatives with affective disorders (first quartile).

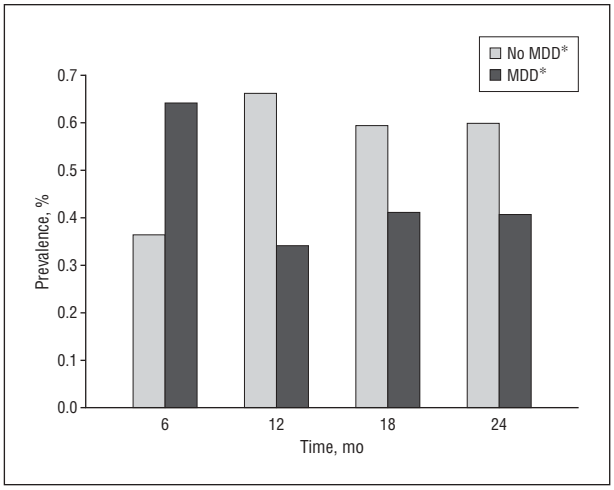

Figure 2. Rates of major depressive disorder (MDD) occurrence at follow-up in preschoolers with depression at baseline. *Excludes missing data.

(Wald $\chi^2=10.77$; OR, 3.64; 95% CI, 1.68-7.88; $P=.001$) and family history of affective disorders at baseline (Wald $\chi^2=14.70$; OR, 1.07; 95% CI, 1.03-1.10; $P<.001$) at baseline were the strongest predictors of subsequent MDD, followed by disruptive disorders at baseline (Wald $\chi^2=7.44$; OR, 3.04; 95% CI, 1.37-6.77; $P=.006$) (Table 2).

MDD COURSE OVER 24 MONTHS

Of 75 total preschoolers with MDD at baseline, 54 completed the MDD module of the PAPA in at least 3 of the next 4 possible data collection waves (6, 12, 18, and 24 months following baseline). Within this subsample, the percentage of depressed children at baseline who were having an episode (either remaining depressed or having a recurrent episode after a period without one) at subsequent study waves were 64% at 6 months, 34% at 12 months, 41% at 18 months, and 40% at 24 months (**Figure 2**). Overall, 10 participants (19%) had a chronic course of depression, which was defined as having an MDD diagnosis at 4 or more assessment points. During the 24-month period, 46% of preschoolers who had depression at baseline recovered and had no additional MDD episodes during the 24-month study period. Thirty-five percent of preschoolers depressed at baseline recovered (did not have an episode for a ≥6-month period) and then had a recurrence at a later data collection wave.

BASELINE MDD SEVERITY IN DEPRESSED GROUPS WITH DIFFERING COURSES

Figure 3 illustrates mean MDD severity scores across the 24-month period. Based on these descriptive data, preschoolers who were depressed at baseline were classified into 1 of 3 depression trajectories: (1) chronic (n=10), defined as being in episode at 4 or more assessment points; (2) recovered with subsequent recurrence (n=19), defined as being in episode at 2 points separated by a period of at least 6 months out of episode; and (3) recovered (n=25), defined as being in episode at baseline only, or baseline and subsequent contiguous points, followed by being out of episode with no additional episodes during the follow-up period. In addition, MDD severity scores at 3 annual study waves for the psychiatric group (n=76) and the no-disorder group, defined by no disorders at all 3 waves (n=77), were also compared. Due to excessive missing data at 6 and 18 months, depression severity scores were compared among groups at the 3 annual waves only.

Using a repeated-measure ANOVA, significant differences in MDD severity scores at all 3 annual waves were found among the 3 depressed groups (Wilks' $\lambda=0.615$,

$F_{2,47}=14.727$, $P<.001$). While there were differences between groups at all points, some of these were confounded by whether or not those in the recovered/recurred and recovered groups were having an episode at 12 and 24 months. However, at baseline, the chronic depressed group had significantly ($t=2.33$, $P=.03$) higher MDD severity scores than the recovered group (who were all depressed at baseline) but not than the recovered/recurred group (who were also all depressed at baseline) ($t=1.78$, $P=.08$) (**Table 3**).

MDD SEVERITY IN RECOVERED DEPRESSED AND NONDEPRESSED GROUPS

Preliminary analyses indicated an inequality of both covariance matrices and error variances between the depressed groups and nondepressed comparison groups. Thus, analyses that examined differences between depression severity scores among the recovered depressed group and the 2 nondepressed (psychiatric disorder and no-disorder) groups were conducted using nonparametric methods (Kruskal-Wallis test and Mann-Whitney *U* test). Again, significant differences in MDD severity scores at all 3 annual waves were found. These overall findings may be confounded by unclear depression status at each wave for 2 groups. However, Mann-Whitney *U* tests showed that the recovered depressed group had significantly higher MDD severity scores than the no-disorder group at 24 months ($z=2.08$, $P=.04$) when all subjects in the group with MDD previously were in recovery. In addition, the psychiatric group had significantly higher MDD severity scores than the no-disorder group at baseline ($z=-3.51$, $P<.001$), 12 months ($z=-2.24$, $P=.03$), and 24 months ($z=-3.10$, $P=.002$).

MDD CHRONICITY/RECURRENCE IN PRESCHOOL-AGED CHILDREN

A multinomial logistic regression was conducted to examine whether key risk factors known to determine course in older children with depression were also associated with the 24-month course (chronicity/recovery) of preschool depression. The dependent variable was the 3 MDD course groups (chronic, recovered/recurred, and recovered). The variables entered into the model included demographic characteristics (children's age in months and sex), children's comorbid diagnoses, stressful life events, baseline MDD severity, as well as maternal and family history of affective disorders. The overall model was not significant ($\chi^2_{22}=20.22$, $P=.57$).

COMMENT

Study findings demonstrated that preschool MDD showed homotypic continuity throughout a 24-month follow-up. That is, MDD at baseline, more than any other baseline disorder, predicted later MDD; conversely, MDD at baseline predicted later MDD more strongly than it predicted other later disorders. Perhaps most importantly, findings demonstrated that even after controlling for comorbid disorders and other demographic variables and risk factors, preschoolers with depression had a 4 times greater likelihood of MDD 12 and/or 24 months later than preschoolers without depression. Preschool MDD as well as family history of affective disorders emerged as the most robust predictors of later MDD compared with other risk factors considered simultaneously in the model. Preschool MDD also showed a chronic and recurrent course during 24 months. Specifically, 57% of preschoolers with depression had an episode in 2 or more study waves, and 18% had a chronic course (had an episode in ≥4 or more study waves) during the 2-year study period. These findings add 24-month longitudinal stability to the database, validating the occurrence of MDD during the preschool period. The evidence of homotypic continuity refutes the notion that preschool MDD is a nonspecific precursor of later psychopathology.

Our study is the first available, to our knowledge, to follow-up and describe the 2-year course of preschool MDD in a large systematically assessed sample. Study findings demonstrated that the 24-month course of preschool MDD was similar to the course known in the school-age form of

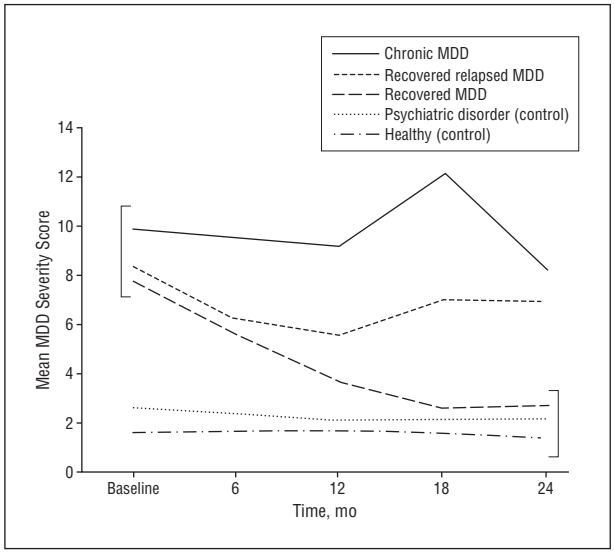

Figure 3. Comparison of mean major depressive disorder (MDD) severity scores across study waves in 3 depression groups (chronic, recovered/recurred, and recovered), other psychiatric disorder group, and no-disorder group. The figure presents 5 waves of mean MDD severity scores for 3 depressed groups and only 3 annual waves (baseline, 12 months, and 24 months) of mean MDD severity scores for psychiatric control and no-disorders groups (owing to data collection). At 6 and 18 months, excessive data were missing from recovered and chronic groups, so MDD severity scores comparisons were only conducted for 3 annual waves.

Table 3. Depression Severity Scores at Baseline and 24 Months

	Depression Severity Score, Mean (SD)	
Group	Baseline	Follow-up at 24 Months
Chronic	9.90 (2.96)	8.22 (3.42)
Recovered/recurred	8.37 (3.02)	7.00 (3.51)
Recovered	7.72 (2.41)	2.71 (2.58)
Psychiatric disorder control	2.62 (1.83)	2.18 (1.63)
No disorder, all waves	1.62 (1.50)	1.42 (1.45)

the disorder. While other risk factors for later MDD were found, early MDD itself and family history of affective disorder were the most powerful risk factors for later MDD. Of interest was that disruptive disorders, and not anxiety disorders, during the preschool period predicted later MDD. The finding that disruptive disorders are associated with later depression has been reported in school-age samples.[41] However, this finding differs from the pattern demonstrated during school age and adolescence in which early anxiety is a known harbinger of later MDD.[42,43] One explanation for developmental differences may be that early disruptive disorders are associated with social impairment and peer rejection that lead to later MDD, while some early anxiety disorders more common during the preschool period (eg, separation anxiety) are self-limited. Another possible reason for these discrepant findings is the relatively short follow-up period of the study. However, the risk of MDD after a preschool-onset disruptive disorder suggests that clinicians should maintain vigilance for this outcome. Further investigation of these patterns of heterotypic continuity between preschool-onset anxiety and disruptive disorders and later childhood MDD are indicated.

These findings add to the growing database validating preschool MDD and distinguishing it from other early-onset disorders. It was also notable that diagnostic data for this investigation were based on an independent, age-appropriate, interviewer-based psychiatric interview (the PAPA) different than that used in the first set of investigations (Diagnostic Interview Schedule for Children, Version IV–Young Child), adding further weight to these data contributing to the growing database validating preschool MDD. Study findings underscore the clinical and public health importance of identification and treatment of MDD as early as the preschool period. Study findings also suggest that further investigation of this understudied early childhood disorder is warranted.

Of note was that the depressed preschoolers who demonstrated a chronic 24-month course had the highest MDD severity scores at baseline, which suggests that a more severe depressive episode is a harbinger of greater chronicity in early childhood. Also of interest was that preschoolers who had recovered from MDD still had higher MDD severity scores than controls with psychiatric disorders and no disorders, suggesting that a relatively high number of residual depressive symptoms were still manifest even during periods of recovery. The finding of residual depressive symptoms during recovery has also been reported in adult MDD.[44,45] Longitudinal investigations of adults with residual depressive symptoms have shown earlier recurrence and continued impairment in social functioning in follow-up studies.[46-48] The implications of this finding will be clarified as this preschool sample is observed into later childhood and early adolescence. Although the model that tested risk factors that impact course was not significant, these negative findings should be viewed with caution owing to the relatively short follow-up period. Therefore, later testing of this model over a longer follow-up period will be important.

This study is limited by the reliance on parent informants for diagnostic determinations. Although child reports and observational data were obtained, these data were not yet available and will be the focus of future investigations. However, previous study findings have demonstrated validation for parent-based diagnoses from correlations with teacher and child reports as well as associations with biological findings.[24,27,29,35] Another limitation is the relatively short follow-up period and the fact that the sample was screened and thus not representative. In addition, the interview did not assess onsets and offsets of depressive episodes. Longitudinal follow-up data at later school age and early adolescence are currently being obtained in this ongoing investigation.

These findings of homotypic continuity of preschool-onset MDD have important clinical implications. Despite some promising findings, safe and effective treatments for school-age MDD remain largely elusive.[49-54] Based in part on the recurrent course and the relative treatment resistance of childhood MDD, there has been increased interest in the identification of the disorder at the earliest possible stage of development. The potential public health importance of identification of preschool MDD is underscored by the established unique efficacy of early intervention during the preschool period in other childhood disorders.[55,56] Therefore, study findings that demonstrate longitudinal stability and homotypic continuity of preschool MDD suggest that earlier interventions for MDD during the preschool period may be an important area for investigation in the search for more effective treatments for childhood MDD.

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Correspondence: Joan L. Luby, MD, Department of Psychiatry, Washington University School of Medicine, 660 S Euclid Ave, Box 8134, St Louis, MO 63110 (lubyj@psychiatry.wustl.edu).
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REFERENCES

1. Costello EJ, Pine DS, Hammen C, March JS, Plotsky PM, Weissman MM, Biederman J, Goldsmith HH, Kaufman J, Lewinsohn PM, Hellander M, Hoagwood K, Koretz DS, Nelson CA, Leckman JF. Development and natural history of mood disorders. *Biol Psychiatry*. 2002;52(6):529-542.
2. Kaufman J, Martin A, King RA, Charney D. Are child-, adolescent-, and adult-onset depression one and the same disorder? *Biol Psychiatry*. 2001;49(12):980-1001.
3. Moreno C, Roche AM, Greenhill LL. Pharmacotherapy of child and adolescent depression. *Child Adolesc Psychiatr Clin N Am*. 2006;15(4):977-998, x.
4. Ryan ND. Treatment of depression in children and adolescents. *Lancet*. 2005;366(9489):933-940.
5. Kovacs M, Feinberg TL, Crouse-Novak MA, Paulauskas SL, Finkelstein R. Depressive disorders in childhood, I: a longitudinal prospective study of characteristics and recovery. *Arch Gen Psychiatry*. 1984;41(3):229-237.
6. Kovacs M, Feinberg TL, Crouse-Novak M, Paulauskas SL, Pollock M, Finkelstein R. Depressive disorders in childhood, II: a longitudinal study of the risk for a subsequent major depression. *Arch Gen Psychiatry*. 1984;41(7):643-649.
7. McCauley E, Myers K, Mitchell J, Calderon R, Schloredt K, Treder R. Depression in young people: initial presentation and clinical course. *J Am Acad Child Adolesc Psychiatry*. 1993;32(4):714-722.
8. Rao U, Weissman MM, Martin JA, Hammond RW. Childhood depression and risk of suicide: a preliminary report of a longitudinal study. *J Am Acad Child Adolesc Psychiatry*. 1993;32(1):21-27.
9. Sadock B, Sadock V. *Kaplan & Sadock's Synopsis of Psychiatry: Mood Disorders and Suicide in Children and Adolescents*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:1262.

10. Birmaher B, Ryan ND, Williamson D, Brent DA, Kaufman J, Dahl RE, Perel J, Nelson B. Childhood and adolescent depression: a review of the past 10 years, part I. *J Am Acad Child Adolesc Psychiatry*. 1996;35(11):1427-1439.
11. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301(5631):386-389.
12. Kaufman J, Yang BZ, Douglas-Palumberi H, Houshyar S, Lipschitz D, Krystal JH, Gelernter J. Social supports and serotonin transporter gene moderate depression in maltreated children. *Proc Natl Acad Sci U S A*. 2004;101(49):17316-17321.
13. Kovacs M, Devlin B, Pollock M, Richards C, Mukerji P. A controlled family history study of childhood-onset depressive disorder. *Arch Gen Psychiatry*. 1997;54(7):613-623.
14. Kovacs M, Obrosky DS, Gatsonis C, Richards C. First-episode major depressive and dysthymic disorder in childhood: clinical and sociodemographic factors in recovery. *J Am Acad Child Adolesc Psychiatry*. 1997;36(6):777-784.
15. Kashani JH, Ray JS. Depressive related symptoms among preschool-age children. *Child Psychiatry Hum Dev*. 1983;13(4):233-238.
16. Kashani JH, Ray JS, Carlson GA. Depression and depressive-like states in preschool-age children in a child development unit. *Am J Psychiatry*. 1984;141(11):1397-1402.
17. Kashani JH, Carlson GA. Major depressive disorder in a preschooler. *J Am Acad Child Psychiatry*. 1985;24(4):490-494.
18. Kashani JH, Holcomb WR, Orvaschel H. Depression and depressive symptoms in preschool children from the general population. *Am J Psychiatry*. 1986;143(9):1138-1143.
19. Rie HE. Depression in childhood: a survey of some pertinent contributions. *J Am Acad Child Psychiatry*. 1966;5(4):653-685.
20. Stalets MM, Luby JL. Preschool depression. *Child Adolesc Psychiatr Clin N Am*. 2006;15(4):899-917, viii-ix.
21. Lavigne JV, Arend R, Rosenbaum D, Binns HJ, Christoffel KK, Gibbons RD. Psychiatric disorders with onset in the preschool years, I: stability of diagnoses. *J Am Acad Child Adolesc Psychiatry*. 1998;37(12):1246-1254.
22. Luby J, Heffelfinger AK, Mrakotsky C, Hessler MJ, Brown KM, Hildebrand T. Preschool major depressive disorder: preliminary validation for developmentally modified DSM-IV criteria. *J Am Acad Child Adolesc Psychiatry*. 2002;41(8):928-937.
23. Egger HL, Angold A. Common emotional and behavioral disorders in preschool children: presentation, nosology, and epidemiology. *J Child Psychol Psychiatry*. 2006;47(3-4):313-337.
24. Luby JL, Belden AC, Pautsch J, Si X, Spitznagel E. The clinical significance of preschool depression: impairment in functioning and clinical markers of the disorder. *J Affect Disord*. 2009;112(1-3):111-119.
25. Luby JL, Heffelfinger AK, Mrakotsky C, Brown KM, Hessler MJ, Wallis JM, Spitznagel EL. The clinical picture of depression in preschool children. *J Am Acad Child Adolesc Psychiatry*. 2003;42(3):340-348.
26. Luby JL, Mrakotsky C, Heffelfinger A, Brown K, Hessler M, Spitznagel E. Modification of DSM-IV criteria for depressed preschool children. *Am J Psychiatry*. 2003;160(6):1169-1172.
27. Luby JL, Heffelfinger A, Mrakotsky C, Brown K, Hessler M, Spitznagel E. Alterations in stress cortisol reactivity in depressed preschoolers relative to psychiatric and no-disorder comparison groups. *Arch Gen Psychiatry*. 2003;60(12):1248-1255.
28. Luby JL, Mrakotsky C, Heffelfinger A, Brown K, Spitznagel E. Characteristics of depressed preschoolers with and without anhedonia: evidence for a melancholic depressive subtype in young children. *Am J Psychiatry*. 2004;161(11):1998-2004.
29. Luby JL, Sullivan J, Belden A, Stalets M, Blankenship S, Spitznagel E. An observational analysis of behavior in depressed preschoolers: further validation of early-onset depression. *J Am Acad Child Adolesc Psychiatry*. 2006;45(2):203-212.
30. Mol Lous A, de Wit CA, De Bruyn EE, Riksen-Walraven JM. Depression markers in young children's play: a comparison between depressed and nondepressed 3- to 6-year-olds in various play situations. *J Child Psychol Psychiatry*. 2002;43(8):1029-1038.
31. Lavigne JV, Arend R, Rosenbaum D, Binns HJ, Christoffel KK, Gibbons RD. Psychiatric disorders with onset in the preschool years, II: correlates and predictors of stable case status. *J Am Acad Child Adolesc Psychiatry*. 1998;37(12):1255-1261.
32. Mesman J, Koot HM. Early preschool predictors of preadolescent internalizing and externalizing DSM-IV diagnoses. *J Am Acad Child Adolesc Psychiatry*. 2001;40(9):1029-1036.
33. Caspi A. The child is father of the man: personality continuities from childhood to adulthood. *J Pers Soc Psychol*. 2000;78(1):158-172.
34. Luby J, Heffelfinger A, Mrakotsky C, Hildebrand T. *Preschool Feelings Checklist*. St Louis, MO: Washington University; 1999.
35. Luby JL, Heffelfinger A, Koenig-McNaught A, Brown K, Spitznagel E. The preschool feelings checklist: a brief and sensitive screening measure for depression in young children. *J Am Acad Child Adolesc Psychiatry*. 2004;43(6):708-717.
36. Egger HL, Ascher B, Angold A. *Preschool Age Psychiatric Assessment (PAPA): Version 1.1*. Durham, NC: Center for Developmental Epidemiology, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center; 1999.
37. Egger HL, Erkanli A, Keeler G, Potts E, Walter B, Angold A. Test-retest reliability of the Preschool Age Psychiatric Assessment (PAPA). *J Am Acad Child Adolesc Psychiatry*. 2006;45(5):538-549.
38. Costello EJ, Angold A, March J, Fairbank J. Life events and post-traumatic stress: the development of a new measure for children and adolescents. *Psychol Med*. 1998;28(6):1275-1288.
39. Angold A, Prendergast M, Cox A, Harrington R, Simonoff E, Rutter M. The Child and Adolescent Psychiatric Assessment (CAPA). *Psychol Med*. 1995;25(4):739-753.
40. Maxwell E. *Manual for the FIGS*. Bethesda, MD: Clinical Neurogenetics Branch; 1992.
41. Burke JD, Loeber R, Lahey BB, Rathouz PJ. Developmental transitions among affective and behavioral disorders in adolescent boys. *J Child Psychol Psychiatry*. 2005;46(11):1200-1210.
42. Capaldi DM. Co-occurrence of conduct problems and depressive symptoms in early adolescent boys, II: a 2-year follow up at grade 8. *Dev Psychopathol*. 1992;4(1):125-144.
43. Pine DS, Cohen P, Brook J. Adolescent fears as predictors of depression. *Biol Psychiatry*. 2001;50(9):721-724.
44. Fava GA, Fabbri S, Sonino N. Residual symptoms in depression: an emerging therapeutic target. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26(6):1019-1027.
45. Judd LL, Paulus MJ, Schettler PJ, Akiskal HS, Endicott J, Leon AC, Maser JD, Mueller T, Solomon DA, Keller MB. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am J Psychiatry*. 2000;157(9):1501-1504.
46. Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Paulus MP, Kunovac JL, Leon AC, Mueller TI, Rice JA, Keller MB. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. *J Affect Disord*. 1998;50(2-3):97-108.
47. Judd LL, Akiskal HS, Zeller PJ, Paulus M, Leon AC, Maser JD, Endicott J, Coryell W, Kunovac JL, Mueller TI, Rice JP, Keller MB. Psychosocial disability during the long-term course of unipolar major depressive disorder. *Arch Gen Psychiatry*. 2000;57(4):375-380.
48. Kennedy N, Paykel ES. Residual symptoms at remission from depression: impact on long-term outcome. *J Affect Disord*. 2004;80(2-3):135-144.
49. Brent DA. Glad for what TADS adds, but many TADS grads still sad. *J Am Acad Child Adolesc Psychiatry*. 2006;45(12):1461-1464.
50. Compton SN, March JS, Brent D, Albano AM V, Weersing R, Curry J. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. *J Am Acad Child Adolesc Psychiatry*. 2004;43(8):930-959.
51. Emslie GJ, Rush J, Weinberg W, Kowatch R, Hughes C, Carmody T, Rintelmann J. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*. 1997;54(11):1031-1037.
52. Emslie GJ. Improving outcome in pediatric depression. *Am J Psychiatry*. 2008;165(1):1-3.
53. Hughes CW, Emslie GJ, Crismon ML, Posner K, Birmaher B, Ryan N, Jensen P, Curry J, Vitiello B, Lopez M, Shon SP, Pliszka SR, Trivedi MH; Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(6):667-686.
54. Wagner KD. Pharmacotherapy for major depression in children and adolescents. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(5):819-826.
55. Fenske EC, Zalenski S, Krantz PJ, McClanahan LE. Age at intervention and treatment outcome for autistic children in a comprehensive intervention program. *Analysis Intervent Dev Disabilities*. 1985;5:49-58.
56. Eyberg SM, Boggs SR, Algina J. Parent-child interaction therapy: a psychosocial model for the treatment of young children with conduct problem behavior and their families. *Psychopharmacol Bull*. 1995;31(1):83-91.