Grandparents, Parents, and Grandchildren at High Risk for Depression: A Three-Generation Study

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ABSTRACT

Objective: High-risk studies of psychiatric disorders in parents and offspring that include 3 generations are uncommon. Multigenerational studies can be clinically useful as they can provide information for risk prediction from one generation to another for the development of empirically based interventions. Using a high-risk design, this study examines the association of grandparent major depressive disorder (MDD) and parent MDD with psychopathology in grandchildren. **Method:** Using Cox proportional hazards in a sample of 90 grandchildren at high and low risk for depression by virtue of their grandparents' and parents' depression status, the authors examined the risk for offspring depression and anxiety. **Results:** Grandparent and parent MDD were associated with grandchild anxiety (relative risk [RR] = 5.51 and RR = 3.09, respectively). Grandchildren with both a depressed parent and grandparent had the highest risk for anxiety. Parental MDD is associated with an increased risk for grandchild disruptive disorder (RR = 10.77). Forty-nine percent of the grandchildren in families in which both the parent and grandparent were depressed had some form of psychopathology. The grandchildren from those families were the most impaired. **Conclusions:** Prepubertal-onset anxiety disorder is a risk factor for the later development of clinically significant recurrent MDD across several generations of families at high risk for depression. Parental impaired functioning increases the risk for disruptive disorders. Children in families with multiple generations of depression are at particularly high risk for some form of psychopathology. *J. Am. Acad. Child Adolesc. Psychiatry*, 1999, 38(3):289–296. **Key Words:** depression, anxiety, disruptive disorders, multigenerational, children.

High-risk studies of psychiatric disorders in parents and offspring that include 3 generations are uncommon (Kovacs et al., 1997; Orvaschel, 1990). Multigenerational studies can be clinically useful as they can provide information for risk prediction from one generation to another which can be used not only in genetic studies but for the development of empirically based interventions as well.

We have been following the offspring of depressed and nondepressed parents for 10 years. All of the offspring are now adults and have their own children (the grandchildren of the original cohort). This has provided an opportunity to study rates and patterns of transmission of psychopathology across generations as well as early signs of psychopathology (because the grandchildren are relatively young) and to determine the comparability of risk across the generations.

The main findings from the study of the parents (the second generation) of the grandchildren (the third generation) is that anxiety symptoms are the earliest presentation of psychiatric disorder (often before puberty) in the parents and that early anxiety symptoms increase the risk for subsequent depression. These findings are consistent with retrospective reports of age at onset and sequence of disorders in adults (Breslau et al., 1995; Parker et al., 1997); with community-based longitudinal studies of children and youth (Angst et al., 1997; Pine et al., 1998); and with high-risk studies of offspring of depressed compared with nondepressed parents or psychiatrically ill controls. These latter studies consistently show that high-risk compared with low-risk offspring are at increased risk for major depressive disorder (MDD) as well as anxiety (Beidel and Turner, 1997; Breslau et al., 1988; Hammen et al., 1990; Keller et al., 1986;

Accepted September 16, 1998.

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This work was partially supported by NIMH grants MH-36197 and 5P50 MH-43878-08.

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Orvaschel et al., 1988; Warner et al., 1995; Weissman et al., 1997) and that anxiety disorders usually come first. Only the Orvaschel, Hammen, and Weissman studies have a longitudinal design (18-month, 3-year, and 10-year follow-up, respectively), so that the course of the disorders can be observed directly.

If there is continuity across the generations, on the basis of our prior findings we would expect that the grandchildren of depressed grandparents will follow a course similar that of to their parents, with early anxiety symptoms and higher rates of MDD. The hypotheses being tested are the following: (1) grandchildren of depressed compared with nondepressed grandparents and/or parents will be at increased risk for depression and anxiety; and (2) grandchildren with both a depressed grandparent and a parent with MDD will have the highest rates of MDD and anxiety.

METHOD

Sample

The probands and the spouses of the probands will be referred to as the grandparents; the offspring of the probands as the parents; the spouses of the parents as spouses; and the offspring of the parents as the grandchildren. Parents were initially selected for the presence or absence of a lifetime history of major depression (based on Research Diagnostic Criteria [RDC]) in the grandparents. A complete description of the grandparents and the assessment has been published elsewhere (Weissman et al., 1982, 1992, 1997). The depressed grandparents had received treatment at Yale University Depression Research Unit (New Haven, CT). The nondepressed grandparents came from a 1975 community survey conducted in New Haven.

Ten years after the initiation of the study (time 10), families were contacted for a reassessment. Of the 260 parents, 222 (86%) were reinterviewed at time 10. Seventy-three (84%) grandparents and 52 (85%) spouses of the grandparents were also reinterviewed. There were no significant differences in the attrition rate of grandparents by grandparent diagnostic status, age, socioeconomic status of the family, or gender. At time 10, the grandparents had 175 grandchildren. To be eligible for interview the grandchildren had to be older than 5 years of age, living in the geographic area of the study, or 18 years of age or older if a telephone interview was required. Of the 175 grandchildren, 119 were eligible to be interviewed. One grandchild was dead. Ninety (76%) of the remaining 118 grandchildren were interviewed directly or had informant interviews with the parent. Four of the grandchildren were not biologically related to the grandparent (i.e., they were stepchildren) and were eliminated from these analyses. Thirty-three (70%) of the 47 parents' spouses were interviewed. There were no significant differences in response rate of the grandchildren by gender, age of grandchild, or parent or grandparent depression status. The 90 grandchildren interviewed did not differ from the grandchildren not old enough to be interviewed by gender of grandchild, parental depression status, or grandparent depression status. The mean and median age of the grandchildren too young to be interviewed was 3 years of age (SD = 1.2). The mean and median age at interview of the interviewed grandchildren was 10 years (SD = 3.9). Seventy percent of the grandchildren interviewed were 12 years of age or younger. Only 4 grandchildren were 18 years of age or older. Attrition of parents did not differ by grandparent diagnostic status, parent diagnostic status, family socioeconomic status, or gender of parent. However, at time 10, older parents were more likely than younger parents to be interviewed (mean: 28.5 versus 26.4 years of age; $t = -2.09$, $df = 54.9$, $p = .04$). There were 2 first onsets of major depression in the spouses of the grandparents in the nondepressed group between time 2 and 10. We reassigned these families to the grandparent depressed group.

Assessment

Grandparents, parents, parents' spouses, and grandchildren 18 years of age or older were directly and independently interviewed with the Schedule for Affective Disorders and Schizophrenia-Lifetime version modified to include RDC, *DSM-III*, and *DSM-III-R* criteria (Mannuzza et al., 1986). Grandchildren younger than the age of 18 were directly interviewed with a revised version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic version (Orvaschel et al., 1982). The period of assessment for the parents and grandparents was from the last time of interview until the present and lifetime for the grandchild and spouse of parent. In addition, the parent was interviewed about the grandchild. Seventy-three grandchildren were directly interviewed and 89 had informant interviews. Sixty-nine had both informant and direct interviews. Eighteen had informant-only interviews, primarily because they were too young for telephone interviews and 3 had direct interviews only. Those grandchildren directly interviewed who were older than 7 years were asked to complete a self-report measure. Sixty-three grandchildren filled out a self-report inventory. Parents filled out a battery of instruments on 75% (132/175) of the grandchildren (regardless of interview status).

Interviewers and Best-Estimate Procedures

Interviewers (doctoral- and master's-level experienced mental health professionals) were located in Connecticut, where most of the subjects lived. Details on training, monitoring, reliability, and procedures are provided elsewhere (Weissman et al., 1997). Diagnoses of offspring were based on the best-estimate procedure (Leckman et al., 1982). To derive best-estimate diagnoses, an experienced clinician who was not involved in the interviewing, independently and blind to the diagnostic status of the parent and the previous assessments, reviewed all available information and assigned a *DSM-III-R* diagnosis for each offspring.

The diagnoses used for this study were cumulative across times 1, 2, and 10. At times 1 and 2, *DSM-III* criteria were used for the parents and National Institute of Mental Health RDC criteria were used for the grandparents. At time 10, *DSM-III-R* criteria at the probable or definite level of certainty were used for grandchildren. *DSM-III-R* criteria at the definite level of certainty were used for the parents, spouses, and grandparents. In addition, best estimators rated the adults on the Global Assessment Scale (GAS) (Endicott et al., 1976) and the grandchildren on the Children's Global Assessment Scale (C-GAS) (Shaffer et al., 1983). The scale is a measure of overall functioning that is rated on a 0 to 100 scale with higher scores indicating better adjustment.

Statistical Analysis

Initially, univariate analyses to test for the association of grandparent and parent depression with grandchild diagnosis and C-GAS scores were performed as follows: Group differences by parent and

grandparent depression status for outcome variables were tested using χ^2 tests for categorical variables and t tests for continuous variables. The univariate analyses were followed by multivariate analyses to estimate the effect of potential confounders. Cox proportional hazards regression models were fit with grandchild diagnoses as outcomes and alternately grandparent or parent depression as predictors (Cox, 1972; Cox and Oakes, 1984). Analysis of covariance (ANCOVA) models were fit with the C-GAS score as the outcome and grandparent or parent MDD alternately as predictors (Kleinbaum et al., 1988). Age and gender of the grandchild were consider a priori to be potential confounders and were retained in every model.

Models were fit with grandparent MDD, parent MDD, grandchild gender, and grandchild age to examine whether there was an effect of parent MDD after controlling for grandparent MDD and an effect of grandparent MDD after controlling for parent MDD. This was followed by conducting a formal test for interaction between grandparent and parent MDD which involved entering an interaction term into the model. It was determined whether the interaction term made a statistically significant contribution to the model through the use of one or more of the following: the likelihood ratio test, partial F test, and/or Wald tests of significance. To explore further the potential for interaction between parent and grandparent MDD, Cox proportional hazards regression and ANCOVA models with parental MDD, gender, and age of the grandchildren were fit separately for families with and without grandparent MDD.

Potential confounders were handled as follows: initially it was determined whether they met criteria for a confounder (i.e., they were associated with either parent or grandparent MDD and the outcome), and if they met criteria for a confounder then they were entered into the models to determine whether the confounders explained the association of parent and/or grandparent MDD with the outcome of interest (i.e., grandchild diagnosis or C-GAS). The confounder was considered to make a significant contribution to the model if there was an appreciable change in the β coefficient (i.e., at least 10%) for grandparent or parent MDD without a substantial increase in the corresponding standard error. For the Cox proportional hazards models the change in −2 log likelihood for the full and reduced models was examined to determine whether the confounder made a significant contribution to the model (Hosmer and Lemeshow, 1989). Similarly, a partial F test was used to compare the full and reduced ANCOVA models (Kleinbaum et al., 1988). There was no evidence of a statistically significant interaction between any of the confounders and parent or grandparent MDD.

RESULTS

Demographics

Grandchildren with depressed and nondepressed grandparents did not vary by gender (51% female) but did differ on age (mean age in years [SE] = 11.2 [4.2] versus 9.3 [2.6]; $t = -2.56$, $df = 80.4$, $p = .01$). The age and gender of the grandchild did not vary by parental depression status.

Parents from families in which either grandparent (their parents) was depressed compared with no grandparent depressed did not vary on gender, education, religion, current marital status, level of employment, or income. Depressed compared with nondepressed parents did not vary by age, gender, education, religion, income, marital status, or level of employment.

Diagnoses

After controlling for age and gender of the grandchild, grandchildren of depressed compared with nondepressed grandparents were at increased risk for any anxiety (5-fold). Grandchildren of depressed compared with nondepressed parents were at increased risk for anxiety disorder (3-fold) and disruptive disorders (10-fold) and were more impaired as measured by the C-GAS (Table 1).

Parent MDD, grandparent MDD, and age and gender of grandchild were subsequently entered simultaneously into Cox proportional hazards regression and ANCOVA models. Parent MDD, after controlling for grandparent MDD, significantly increased the risk for grandchild disruptive disorder and impaired functioning. Grandparent MDD, after controlling for parent MDD, significantly increased the risk for grandchild anxiety (Table 2). Numerous small and zero cell counts as well as multicolinearity made it impossible to successfully fit interaction terms for grandparent and parent MDD for the outcomes any anxiety, phobia, or any mood disorder. The interaction term for parent and grandparent MDD was marginally significant ($p = .08$) when entered into the model with C-GAS as the outcome.

Because of the limitations in fitting the interaction terms as described above, variation in risk for grandchild diagnosis and impairment by parental MDD was further explored by examining these risks stratified by grandparent MDD status. Table 3 shows the results of these analyses. Grandchildren with both a depressed grandparent and parent compared with grandchildren with only a depressed grandparent were 4 times as likely to have an anxiety disorder. There were 5 cases of MDD. Four of the 5 cases of MDD had an onset of anxiety either before or simultaneous with their onset of MDD. Three of the 4 cases of MDD with comorbid anxiety were grandchildren with both a depressed parent and grandparent. The fourth case of MDD with comorbid anxiety had a depressed grandparent and a nondepressed parent. The fifth case of MDD without comorbid anxiety had no history of depression in either the parent or the grandparent. There was considerable overlap between any disruptive disorder, any anxiety, and any mood disorder. Thirty-five percent of the grandchildren

TABLE 1
Best-Estimate *DSM-III-R* Grandchild Diagnoses and C-GAS by Grandparent and Parent MDD Status Separately

	Grandparent Status					Parent Status				
	Neither Depressed	≥1 Depressed				Not Depressed	Depressed			
No. of grandchildren	29	57				35	51			
No. of families	17	31				21	27			
Grandchild diagnoses	*n* (%)	*n* (%)	RR	(95% CI)[a]		*n* (%)	*n* (%)	RR	(95% CI)[a]	
Any mood disorder	2 (6.9)	11 (19.3)	2.04	(0.427, 9.80)		3 (8.5)	10 (19.6)	2.54	(0.692, 9.29)	
Major depression	1 (3.4)	4 (7.0)	1.35	(0.119, 15.38)		2 (5.7)	3 (5.9)	0.875	(0.143, 5.37)	
Dysthymia	1 (3.4)	6 (10.5)	2.09	(0.234, 18.67)		1 (2.9)	6 (11.8)	4.57	(0.544, 38.28)	
Any anxiety	2 (6.9)	18 (31.6)	5.51	(1.27, 23.92)		4 (11.4)	16 (31.4)	3.09	(1.03, 9.28)	
Any phobia	2 (6.9)	13 (22.8)	3.50	(0.777, 15.76)		4 (11.4)	11 (21.6)	2.074	(0.654, 6.54)	
Panic disorder	0 (0.0)	1 (1.8)	0.515	1.00[b]		0 (0.0)	1 (1.19)	0.694	1.00[b]	
OCD	0 (0.0)	1 (1.8)	0.515	1.00[b]		0 (0.0)	1 (1.9)	0.694	1.00[b]	
Separation anxiety	0 (0.0)	3 (5.3)	1.58	0.55[b]		0 (0.0)	3 (5.9)	2.13	0.26[b]	
Overanxious	0 (0.0)	2 (3.5)	1.04	0.55[b]		0 (0.0)	2 (3.9)	1.40	0.51[b]	
PTSD	0 (0.0)	1 (1.8)	0.515	1.00[b]		0 (0.0)	1 (1.9)	0.694	1.00[b]	
Any disruptive	3 (10.3)	9 (15.8)	0.951	(0.235, 3.85)		1 (2.9)	11 (21.6)	10.77	(1.36, 85.50)	
ADD	2 (6.9)	4 (7.0)	0.000	1.00[b]		0 (0.0)	6 (11.8)	4.43	0.08[b]	
ODD	3 (10.3)	5 (8.8)	0.056	1.00[b]		1 (2.9)	7 (13.7)	2.91	0.13[b]	
Conduct disorder	0 (0.0)	5 (8.8)	2.70	0.16[b]		0 (0.0)	5 (9.8)	3.64	0.08[b]	
Alcohol dependence/abuse	0 (0.0)	3 (5.3)	1.58	0.55[b]		0 (0.0)	3 (5.9)	2.13	0.26[b]	
Drug dependence/abuse	0 (0.0)	3 (5.3)	1.58	0.55[b]		0 (0.0)	3 (5.9)	2.13	0.26[b]	
	Mean (SE)	Mean (SE)	*F*	*df*	*p*	Mean (SE)	Mean (SE)	*F*	*df*	*p*
BE C-GAS score[a]	78.6 (2.5)	76.9 (1.8)	0.31	1	.58	82.4 (2.1)	74.1 (1.8)	8.76	1	.004

Note: Step-grandchildren are excluded. Parents are biological children of grandparents. Diagnoses are at the probable or definite level of certainty. C-GAS = Children's Global Assessment Scale; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; ADD = attention deficit disorder; ODD = oppositional defiant disorder; BE = best-estimate; RR = relative risk; CI = confidence interval.

[a] RR and C-GAS score adjusted for age and gender of grandchild using Cox proportional hazards regression models and analysis of covariance models, respectively; χ^2 statistic and *p* values provided when the number of cases was not sufficient to conduct multivariate analyses.

[b] Fisher exact 2-tailed test, $df = 1$.

with any anxiety had a disruptive disorder and 40% had a mood disorder. Fifty-eight percent of the grandchildren with any disruptive disorder had an anxiety disorder and 61% had a mood disorder. Grandchildren with a depressed grandparent and parent compared with a depressed grandparent only were significantly more impaired (Table 3).

The grandchildren with both a depressed parent and grandparent had the highest rate of any psychopathology. Forty-nine percent of the grandchildren with both a depressed parent and grandparent had some form of psychopathology compared with 11% in families with only a depressed grandparent, 17% in families with only a depressed parent, and 23% in families in which neither the parent nor the grandparent was depressed. The rate of grandchild psychopathology in the families in which both the parent and grandparent were not depressed was slightly elevated, probably because of pathology other than depression in the parents, spouses, and grandparents in those families.

Potential Confounders

We examined factors that could explain the clustering of grandchild diagnoses and impairment in families in which either or both the parent and the grandparent were depressed. The factors included grandparent and parent anxiety and drug and/or alcohol disorder; number of grandparent and parent depressive episodes; grandparent and parent history of divorce; age at onset of grandparent and parent MDD; parent GAS score, education, occupation, income, age, and gender; and spouse diagnoses of MDD, anxiety disorder, and drug and/or alcohol disorder.

Of the factors associated with grandparent or parent MDD, only parental anxiety (relative risk = 2.41, 95% confidence interval [CI] = 0.923, 6.29) and grandparent

drug and/or alcohol disorder (relative risk = 2.67, 95% CI = 1.02, 7.03) were associated with grandchild anxiety disorder after controlling for age and gender of the grandchild. Grandparent drug and/or alcohol disorder was associated with overall functioning and with any disruptive disorder in the grandchild. Parental impaired functioning was associated with any disruptive disorder in the grandchild. Grandchildren of grandparents with drug and/or alcohol disorder compared with grandparents without were 4.87 times (95% CI = 1.05, 22.63) as likely to have any disruptive disorder, and for every 10-point decrease in the parent's GAS score there was a 1.62-point (95% CI = 1.09, 2.39) increase in risk for any disruptive disorder.

TABLE 2
Parent MDD and Grandparent MDD Entered Simultaneously, Predicting Grandchild Diagnoses, Controlling for Age and Sex

Outcome and Predictors[a]	β	(SE)	RR	(95% CI)[b]
Any mood disorder				
Parent MDD	0.85	(0.68)	2.34	(0.621, 8.78)
Grandparent MDD	0.50	(0.81)	1.65	(0.337, 8.08)
Major depression				
Parent MDD	−0.21	(0.96)	0.808	(0.122, 5.33)
Grandparent MDD	0.38	(1.29)	1.46	(0.116, 18.37)
Dysthymia				
Parent MDD	1.46	(1.09)	4.30	(0.504, 36.72)
Grandparent MDD	0.469	(1.12)	1.60	(0.177, 14.40)
Any anxiety				
Parent MDD	0.883	(0.57)	2.42	(0.794, 7.37)
Grandparent MDD	1.51	(0.76)	4.55	(1.03, 20.03)
Any Phobia				
Parent MDD	0.52	(0.60)	1.69	(0.521, 5.46)
Grandparent MDD	1.12	(0.78)	3.08	(0.667, 14.17)
Any disruptive disorder				
Parent MDD	2.46	(1.06)	11.72	(1.46, 94.28)
Grandparent MDD	−0.50	(0.72)	0.607	(0.147, 2.50)

BE C-GAS[b]	Mean	(SE)	*F*	*p*
Parent MDD				
No	82.3	(2.1)		
Yes	73.9	(1.9)	8.40	.005
Grandparent MDD				
No	77.7	(2.4)		
Yes	78.5	(1.8)	0.07	.80

Note: Step-granchildreen are excluded. Parents are biological children of grandparents. Diagnoses are at the probable or definite level of certainty. MDD = major depressive disorder; RR = relative risk; CI = confidence interval; BE = best-estimate; C-GAS = Children's Global Assessment Scale.

[a] Outcomes appear in boldface and predictors in lightface type.

[b] RR and C-GAS score adjusted for age and gender of grandchild using Cox proportional hazards regression models and analysis of covariance models, respectively.

Controlling for potential confounders made very little difference in the association between either parent or grandparent MDD and grandchild diagnoses or overall functioning. For all models, neither the likelihood ratio test nor partial *F* test was significant; the change in the β or R^2 was not appreciable; and the standard error for the β coefficient for parent or grandparent MDD depending on the model increased.

DISCUSSION

In summary, we found the following:

1. Grandparent and parent MDD are associated with grandchild anxiety. Grandchildren with a depressed parent and grandparent had the highest risk for anxiety.
2. Parental MDD is associated with an increased risk for grandchild disruptive disorder.
3. Forty-nine percent of the grandchildren in families in which both the parent and grandparent were depressed had some form of psychopathology. In addition, the grandchildren from those families were the most impaired.

These findings in grandchildren are consistent with our findings in their parents when they were younger. At a relatively early age the grandchildren in the high-risk families are exhibiting high rates of anxiety. The rates of psychopathology are greatest in the families in which there is the highest familial loading for depression, i.e., families in which both the parent and the grandparent are depressed. These findings are consistent with our original hypotheses. What is somewhat surprising is that grandparent MDD has a stronger effect on the risk for anxiety in grandchildren than parent MDD. Our expectation was that the effect of the grandparent on the psychopathology in the third generation (the grandchildren) would have been attenuated compared with the effect on the second generation (the parents). In fact, the patterns of diagnoses are very similar to the results from the time 1 interviews with their parents. At time 1, the parents were on average 17 years of age; 39% of the parents from high-risk families had anxiety; and 28% had MDD (Weissman, 1988). The grandchildren are approximately 7 years younger than the parents were at time 1. In the highest-risk families (i.e., both the parent and grandparent are depressed), 40% of the grandchildren have anxiety, 8% have MDD, and 23% have some form of mood disorder. The parents had higher rates of MDD

TABLE 3
Best-Estimate *DSM-III-R* Grandchild Diagnoses and C-GAS by Grandparent and Parent MDD Combined

	Grandparent No MDD Parent MDD					Grandparent MDD Parent MDD				
	No	Yes				No	Yes			
No. of grandchildren	17	12				18	39			
No. of families	10	7				11	20			
Grandchild diagnoses	*n* (%)	*n* (%)	RR	(95% CI)		*n* (%)	*n* (%)	RR	(95% CI)[a]	
Any mood disorder	1 (5.9)	1 (8.3)	1.57	(0.090, 27.40)		2 (11.1)	9 (23.1)	2.77	(0.579, 13.23)	
MDD	1 (5.9)	0 (0.0)	0.0			1 (5.6)	3 (7.7)	1.38	(0.136, 14.02)	
Dysthymia	0 (0.0)	1 (8.3)	∞			1 (5.6)	5 (12.8)	3.27	(0.370, 28.98)	
Any anxiety	2 (11.8)	0 (0.0)	0.0			2 (11.1)	16 (41.0)	4.35	(0.990, 19.11)	
Any phobia	2 (11.8)	0 (0.0)	0.0			2 (11.1)	11 (28.2)	2.95	(0.643, 13.53)	
Panic disorder	0 (0.0)	0 (0.0)	0.0			0 (0.0)	1 (2.6)	∞		
OCD	0 (0.0)	0 (0.0)	0.0			0 (0.0)	1 (2.6)	∞		
Separation anxiety	0 (0.0)	0 (0.0)	0.0			0 (0.0)	3 (7.7)	∞		
Overanxious	0 (0.0)	0 (0.0)	0.0			0 (0.0)	2 (5.1)	∞		
PTSD	0 (0.0)	0 (0.0)	0.0			0 (0.0)	1 (2.6)	∞		
Any disruptive disorder	1 (5.9)	2 (16.7)	2.59	(0.234, 268.63)		0 (0.0)	9 (23.1)	∞		
	Mean (SE)	Mean (SE)	*F*	*df*	*p*	Mean (SE)	Mean (SE)	*F*	*df*	*p*
BE C-GAS score[a]	80.4 (2.7)	78.2 (3.2)	0.28	1	.60	85.0 (3.1)	72.5 (2.1)	10.87	1	.002

Note: Step-grandchildren are excluded. Parents are biological children of grandparents. Diagnoses are at the probable or definite level of certainty. MDD = major depressive disorder; C-GAS = Children's Global Assessment Scale; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; BE = best-estimate; RR = relative risk; CI = confidence interval.

[a] RR and C-GAS score adjusted for age and gender of grandchild using Cox proportional hazards regression models and analysis of covariance models, respectively.

at time 1, partially because the majority were at the peak ages of risk for MDD, from 15 to 20 years of age. In addition, perhaps the attenuation of grandparent effect is greater for MDD than for anxiety disorders. The lowest rates of disorder in the grandchildren are in the families in which only the parent (and not the grandparent) is depressed. The implication is that parent psychopathology, unless it is familial, has a minimal effect on grandchild psychopathology with the possible exception of disruptive disorders. The findings support transmission across generations; however, because of the young age and relatively small size of the sample, this conclusion should be considered tentative.

Our finding that the second generation is at high risk for anxiety is consistent with our prediction and with what others have found (Beidel and Turner, 1997; Orvaschel et al., 1988; Warner et al., 1995; Weissman et al., 1997). These findings are of particular importance in light of others' findings that early anxiety increases the risk for later MDD (Breslau et al., 1995; Parker et al., 1997; Pine et al., 1998). None of these studies included family history data. Breslau et al. (1995) and Parker et al. (1997) included adult samples and collected data retrospectively. Pine et al. (1998) did not include family history data; however, their sample and study design is the most similar to this study. The study was longitudinal and the mean age of the sample was 13 at the first time of data collection. Pine et al. found that overanxious disorder, conduct disorder, and MDD in adolescence increased the risk for adult onset of MDD.

The disruptive disorder findings are consistent with an earlier finding of Orvaschel et al. (1988) that attention deficit disorder occurred at a higher rate in offspring of depressed compared with nondepressed parents. In addition, attention deficit disorder occurred more frequently than the internalizing disorders among male offspring of depressed parents.

The increased risk for disruptive disorders, in this study, is likely to be primarily due to parental MDD and not associated with grandparent MDD (i.e., the original probands). There is no significant association between grandparent MDD and disruptive disorders in the grandchildren, and while the cases of disruptive disorder in the families with depressed grandparents are confined to families with depressed parents as well, there is also approximately a 3-fold increase in risk for

disruptive disorders due to parental MDD in the families without depressed grandparents. Particularly given the small numbers, we do not believe the pattern is consistent with an interaction between grandparent and parent MDD. The explanation for this pattern is likely to be environmental. Controlling for parental impaired functioning and grandparent drug and/or alcohol disorder simultaneously, the 2 potential confounders for any disruptive disorder, decreased the relative risk for parental MDD by nearly 50%. These results are considered tenuous; however, they are suggestive of a different pathway for anxiety and disruptive disorders. A family history of MDD increases the risk for anxiety, and the risk is not influenced by confounders. The risk for disruptive disorders is not increased by family history of MDD and is influenced by confounders. Compared with anxiety, disruptive disorders may be associated with a less severe form of MDD. Particularly given the young age of the sample, the findings may represent behavior on the part of the child to get the attention of a depressed parent or the result of a decrease in supervision and/or discipline due to parental impairment. Disruptive disorders do not appear to be transmitted across generations.

Limitations

The most significant limitation of the study is the limited power to detect significance for some of the complex relationships that may exist in the data and to address the problem of lack of independence between observations. It is conceivable that important interactions exist between grandparent and parent MDD and other diagnostic, family, or demographic factors, and we do not have the power to detect them. As the results demonstrate, however, the magnitude of risk is sufficient to detect significant differences in many of the analyses despite the limited power due to a small sample size. In addition, those findings that are significant are consistent with our findings in their parents.

Clinical Implications

These findings have clinical implications for the detection and possible treatment of prepubertal anxiety disorders. Frequently, anxiety in young children is viewed as inconsequential, a part of normal development, and something that the child will outgrow. Our work with the parents has shown that in high-risk families, early anxiety symptoms are a risk factor for the later development of clinically significant recurrent MDD. The results of this study indicate that these anxiety symptoms are being transmitted across the generations. The results suggest that not only are these children at high risk for anxiety, which predicts later severe depression, but parental impaired functioning leads to these children also having behavioral problems. An implication of these findings is that both pathways need to be addressed when planning intervention with high-risk children. Studies to determine whether treatment of early anxiety can prevent the development of later, more severe psychopathology may be useful.

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Pharmacologic and Psychologic Interventions for Procedural Pain. Anne E. Kazak, PhD, Biancamaria Penati, PhD, Patricia Brophy, MSN, CRNP, Bruce Himelstein, MD

Objective: This study evaluated a combined pharmacologic and psychologic intervention (combined intervention, CI) relative to a pharmacologic-only (PO) intervention in reducing child distress during invasive procedures in childhood leukemia. Predictors of child distress included age, group (CI, PO), and procedural variables (medications and doses, technical difficulty, number of needles required). *Methodology:* This was a randomized, controlled prospective study that compared the PO (n = 45) and CI arms (n = 47), at 1, 6, and >12 months after diagnosis. A cross-sectional control group consisted of parents of 70 patients in first remission before the prospective study. Parent questionnaires, staff and parent ratings, and data on medications administered, technical difficulty of the procedure, and needle insertions were obtained for each procedure. This article reports on the final data point for the project (>12 months). *Results:* Mothers and nurses reported lower levels of child distress in the CI than the PO group. The CI and PO groups showed lower levels of child and parent distress than the cross-sectional control group. Distress decreased throughout the time, and child age was inversely related to distress (younger children had more distress) regardless of group. Child distress was associated with staff perceptions of the technical difficulty of the procedure and with child age, but not with medications administered. *Conclusions:* The data showed that pharmacologic and psychologic interventions for procedural distress were effective in reducing child and parent distress and support integration of the two approaches. Younger children experienced more distress and warranted additional consideration. Staff perceptions of the technical difficulty of procedures were complex and potentially helpful in designing intervention protocols. **Pediatrics** 1998;102:59–66