ARTICLE

Age Effects on Antidepressant-Induced Manic Conversion

Andres Martin, MD, MPH; Christopher Young, MD; James F. Leckman, MD; Chengeto Mukonoweshuro, DMD, MPH; Robert Rosenheck, MD; Douglas Leslie, PhD

Background: Antidepressant drug therapy can precipitate mania in vulnerable individuals, but little is known about the effects of age on this phenomenon.

Objective: To pharmacoepidemiologically evaluate the risk of conversion to mania by antidepressant class and patient age.

Design, Setting, and Patients: Using an administrative national database of more than 7 million privately insured individuals, linked outpatient and pharmacy claims were analyzed for mental health users aged 5 to 29 years (N=87 920).

Main Outcome Measures: The proportion and cumulative hazard of manic conversion were analyzed by antidepressant class and subject age among children, adolescents, and young adults with an anxiety or nonbipolar mood disorder in the United States between January 1, 1997, and December 31, 2001. Manic conversion was defined as a new diagnosis of bipolar illness.

Results: During median follow-up of 41 weeks (range, 8-251 weeks), manic conversion occurred in 4786 patients (5.4%). Multivariate analyses using time-dependent Cox proportional hazards models indicated that an increased risk of manic conversion was associated with antidepressant category vs no antidepressant exposure (hazard ratios: 2.1 for selective serotonin reuptake inhibitors, $P<.001$; 3.8 for "other" antidepressants, $P<.001$; and 3.9 for tricyclic antidepressants, $P=.002$). Antidepressant × age interactions revealed inverse age effects for selective serotonin reuptake inhibitors and other antidepressants ($\beta=-.05$; $P<.001$ for both) but not for tricyclic antidepressants ($\beta=-.02$; $P=.25$). Peripubertal children exposed to antidepressants were at highest risk of conversion (number needed to harm: 10 [95% confidence interval, 9-12] among 10- to 14-year-olds vs 23 [95% confidence interval, 21-25] among 15- to 29-year-olds).

Conclusions: Patient age is an effect modifier on the risk of antidepressant-associated manic conversion. Treatment with antidepressants is associated with highest conversion hazards among children aged 10 to 14 years.

Arch Pediatr Adolesc Med. 2004;158:773-780

From the Child Study Center (Drs Martin, Young, Leckman, and Rosenheck), the Department of Psychiatry (Drs Martin, Leckman, Rosenheck, and Leslie), and the School of Epidemiology and Public Health (Drs Mukonoweshuro, Rosenheck, and Leslie), Yale University School of Medicine, New Haven, Conn; Department of Psychiatry, Case Western Reserve University School of Medicine, Cleveland, Ohio (Dr Young); and the Northeast Program Evaluation Center, West Haven, Conn (Drs Rosenheck and Leslie).

IT HAS LONG BEEN KNOWN THAT antidepressant medications can precipitate mania in vulnerable individuals. Indeed, the monoamine oxidase inhibitor iproniazid, one of the first known antidepressants, was serendipitously discovered as a result of its euphoric and mood-elevating effects on patients treated for tuberculosis.[1] Antidepressant-induced switching (the transition from depression into mania) has been studied in several naturalistic and controlled studies, with rates ranging from 7%[2] to 10%[3,4] and as high as 67%[5] among bipolar patients. A meta-analysis[6] comparing the propensity of different antidepressant drug classes to induce mania among bipolar depressive patients found that tricyclic antidepressants (TCAs) were associated with considerably higher rates (11.2%) than selective serotonin reuptake inhibitors (SSRIs), for which rates were comparable to placebo (3.7% and 4.2%, respectively). In contrast, rates among unipolar depressive patients were low (approximately 1%).

In addition to manic switching, other antidepressant adverse effects on the natural course of mood disorders have been described.[7] Among these, drug-induced (as opposed to spontaneous) cycling[8,9] and cycle acceleration[10,11] are the most widely recognized, even in the context of concurrent treatment with mood stabilizers.[12] Switching and cycle acceleration are characteristics that have been linked to poor long-term outcome in bipolar disorder.[13] Despite these lines of evidence negatively implicating antidepressant drug use in the long-term course of affective illness, the issue is far from settled, as exemplified by at least 2 studies[2,14] that have

found no evidence supporting TCA use as a contributing factor to affective instability in bipolar disorder.

The role of age (particularly of young age) on antidepressant-induced manic switching has received relatively little attention but is of clinical interest—and of potential concern—for several reasons. First, the prevalence of antidepressant drug use among children and adolescents has risen steeply during the past decade,[15-17] even among children as young as 2 to 4 years.[18] Second, the recognition and diagnosis of bipolar disorder, once considered rare earlier than age 18 years, has steadily increased during the same period,[19] as has the use of mood stabilizers in this age group.[17] Although late adolescence is a clear epoch for the onset of bipolar disorder, it is not clear whether this or younger ages may be associated with heightened sensitivity to the untoward effects of antidepressant agents. Third, safety data for the use of antidepressants in children and adolescents largely derive from short-term trials (typically 6-12 weeks); adverse events occurring outside of this time window are not routinely identified.[20] Finally, there has been recent controversy over the potential for antidepressants (such as paroxetine and venlafaxine hydrochloride) to exacerbate suicidal ideation among children.[21,22] Such concerns, which have led to action from British and American regulatory agencies,[23] highlight the fact that serious adverse effects associated with antidepressant drug use may be behavioral and potentially life threatening.

Using a large administrative database, we previously described how, between January 1, 1997, and December 31, 2000, (1) the diagnosis of bipolar disorder increased among mental health service users aged 6 to 17 years from a 1-year prevalence of 1.2% to 1.8% (a 54% change)[24] and (2) the use of antidepressants and mood stabilizers increased from 25% and 5.5% to 28% and 6.2%, respectively (shifts of 12.4% and 13.1%, respectively; $P<.001$ for trend for all comparisons).[25] In this study, we use the same administrative database to examine age effects on antidepressant-associated manic conversion. Given that our main outcome of interest (defined herein as the onset of a new bipolar disorder diagnosis) takes place against the backdrop of these time trends, we used time-to-event statistical modeling to track continuously enrolled individuals in an effort to determine the differential contributions of age, antidepressant drug exposure, and their interactions over time on the likelihood of manic diagnostic conversion.

Because our outcome of interest was based on diagnostic information of an administrative nature, we use the term *manic conversion* throughout rather than the more narrowly defined term *manic switch*, which would have required specific clinical information that is unavailable in this database.

METHODS

STUDY POPULATION

Subjects were included in the MarketScan Research Database (Thomson Medstat, Ann Arbor, Mich), a publicly available fee-for-service medical and prescription claims resource that contains information for individuals nationwide who are insured through the benefit plans of large employers and that includes more than 200 different insurance companies. The working sample consisted of patients aged 5 to 29 years with a primary diagnosis of a depressive or anxiety disorder who had pharmacy claims data available for the 5-year study (January 1, 1997, to December 31, 2001). Individual information was stripped of any personal identifiers, stored anonymously, and exclusively referenced through study-specific unique identifiers, following published guidelines.[26]

ASCERTAINMENT OF DIAGNOSES, EXPOSURES, COVARIATES, AND OUTCOMES

Any claim with an *International Classification of Diseases, Ninth Revision* (*ICD-9*),[27] diagnosis code of 290.00 to 319.99 was considered a mental health claim, regardless of the setting of care. Each individual was assigned to a primary diagnostic category, defined as the one responsible for most of the mental health services during follow-up, as measured by the total number of encounters. We defined 5 mental health disorder categories based on a modified coding scheme[24]: (1) severe depression (*ICD-9* codes 296.20-296.39 and 296.82), (2) mild depression (*ICD-9* codes 300.40-300.59, 301.10, 309.00-309.19, 309.28, 301.12, and 311.00-311.99), (3) anxiety disorders (*ICD-9* codes 300.00-300.39, 307.20-307.23, 308.00-308.99, 309.20-309.24, and 313.00-313.29), (4) bipolar disorder (*ICD-9* codes 296.00-296.19, 296.40-296.81, and 296.89-296.99), and (5) other mental health conditions (the remaining *ICD-9* codes in the mental health range).

Independent variables included patient demographic characteristics (sex and age grouped into five 5-year categories) and 3 measures of illness severity: (1) primary diagnosis (severe depression, mild depression, or anxiety), (2) number of different mental diagnoses in the year, and (3) whether inpatient mental health episodes were incurred during the period of observation.

Only patients with linked pharmacy data were included in the study. Patients with any claims for psychotropic drugs were identified from a comprehensive National Drug Code registry. Psychotropics were assigned to 1 of 6 drug classes following a previous classification scheme.[24,25] For each patient, start and end dates (the latter based on the prescription's day supply) were calculated for all medications. Finally, the sum of different medication categories used (range, 0-8) served as a fourth proxy of illness severity.

The primary outcome of interest was a new diagnosis of bipolar disorder as assessed by 2 or more claims. Whenever the outcome was preceded by the introduction of a mood stabilizer (lithium or an antiepileptic drug other than phenytoin), the earlier event was used to mark the conversion date in subsequent time-dependent analyses. Patients with either outcome occurring within the first 2 months of observation were dropped from the working sample based on the rationale that we were interested in only 1 of 2 main types of adverse behavioral reactions to antidepressant drug treatment that have been described in youngsters.[28] The first type occurs early in treatment (median onset, 28 days), is characterized by anxiety or akathisia, and dissipates soon after drug discontinuation; the second type occurs later in treatment (median onset, 91 days), can more closely resemble manic activation, and often lags after drug discontinuation. By excluding from analysis individuals who converted within the first 2 months of observation, we sought a more stringent definition centered on the latter type, thus minimizing misclassification errors, for example, of akathisia into mania.

STATISTICAL ANALYSIS

Standard univariate analyses (χ^2 and 2-tailed, unpaired t tests) were performed for descriptive purposes. The interval be-

tween study entry (the first visit or pharmacy claim available) and diagnostic conversion or last censored study observation was calculated and expressed in weeks or years. Observations that did not meet the end point definition were censored for analytic purposes. Conversion rates were calculated by dividing the number of outcome events by the number of person-years of observation. Confidence intervals (CIs) for conversion rates were calculated using standard epidemiologic formulas,[29] and the difference in conversion rates across groups was expressed using the evidence-based metrics of number needed to harm (NNH) and associated CIs.[30]

The Kaplan-Meier method was used to examine crude survival rates, and Cox proportional hazards regression analysis was used to adjust for potential confounders. Because of the changing nature of the medications used during the observation period, time-dependent covariates were created for these variables, using prescription start and end dates to construct the required intervals,[31] yielding a total of 397 987 observation periods in the final working data set, a mean of 4.4 per participant. In this way, adjusted hazard ratios and 95% CIs were calculated to establish the contribution of different antidepressant agents on conversion (compared with a nonantidepressant reference category) while controlling for age and confounders, especially illness severity. The stratified nature of the Kaplan-Meier and NNH analyses dictated that only individuals prescribed a single antidepressant class could be included in them, but the Cox models provided adjusted estimates for all individuals, including those taking 2 or more antidepressants during their time of observation.

Given our a priori hypothesis that the effects of antidepressant drug use on manic conversion would differ according to patient age, we included interaction terms to ascertain the role of age as an effect modifier on conversion hazards. To that end, in addition to the main effect models (of age and antidepressant class, models I and II, respectively), antidepressant × age terms were added to interaction models. Age in years was first used in interaction terms for all antidepressants and for each class (models IIIa and IVa, respectively), testing for significance using the Wald χ^2 test. Interactions were then deconstructed by using age as a 5-year category rather than a continuous variable (models IIIb and IVb, respectively). The oldest age group (24-29 years) was selected as the reference category.

RESULTS

There were 4786 converters among the 87 920 patients in the sample, an overall period prevalence of 5.4%. Participants were followed during the 5-year study for a median of 41 weeks (range, 8-251 weeks), for a cumulative total of 79 408 person-years and a conversion rate of 6.0% per year (95% CI, 5.9%-6.2%). The primary outcome was preceded by the introduction of a mood stabilizer in 2766 converters (57.8%), but, as noted earlier, all converters went on to have 2 or more claims with a diagnosis of bipolar disorder.

The study sample was predominantly female (60%) and older (72% of participants were aged 15-29 years). Mild depression was the most common diagnosis (in 54% of participants), followed by anxiety (in 28%), and severe depression (in 19%). Only 201 individuals (2.3 per 1000) had had an inpatient psychiatric hospitalization. A total of 32 864 patients (37.4%) were treated with at least 1 antidepressant medication; although the modal use among the medication-exposed group was of a single antidepressant, 9093 of them (27.7%) used 2 or more different medications (antidepressant or other psychotropic). Demographic and clinical characteristics of the study sample according to conversion status are summarized in **Table 1**.

Table 1. Demographic and Clinical Characteristics of the 87 920 Study Participants*

Characteristic	Converters (n = 4786)	Nonconverters (n = 83 134)	*P* Value†
Sex, No. (%)			
M	1835 (38)	32 832 (39)	.11
F	2951 (62)	50 302 (61)	
Age category, No. (%)			
5-9 y	210 (4)	9600 (12)	<.001
10-14 y	884 (18)	14 111 (17)	
15-19 y	1791 (37)	22 785 (27)	
20-24 y	981 (20)	15 776 (19)	
25-29 y	920 (19)	20 862 (25)	
Diagnosis, No. (%)			
Severe depression	2026 (42)	14 534 (17)	<.001
Mild depression	1988 (42)	45 107 (54)	
Anxiety disorder	772 (16)	23 493 (28)	
Inpatient hospitalization, No. (%)	72 (2)	129 (<1)	<.001
Antidepressant drug use, No. (%)			
None	934 (20)	50 610 (61)	<.001
Any	2932 (61)	29 932 (36)	
SSRI	2329 (49)	24 136 (29)	
Other	1268 (26)	9887 (12)	
Tricyclic	389 (8)	2638 (3)	
Other psychotropic drug use, No. (%)			
α-Agonist	145 (3)	710 (1)	<.001
Antipsychotic			
Atypical	462 (10)	1272 (2)	
Typical	87 (2)	308 (<1)	
Sedative hypnotic	1038 (22)	9955 (12)	
Stimulant	553 (12)	5689 (7)	
Mood stabilizer	2769 (58)	0	
Psychotropic drugs, mean (SD), No.	1.3 (1.3)	0.7 (0.9)	<.001
Diagnoses, mean (SD), No.	2.6 (1.0)	2.1 (0.7)	<.001
Follow-up, mean (SD), wk	41 (43)	47 (39)	<.001

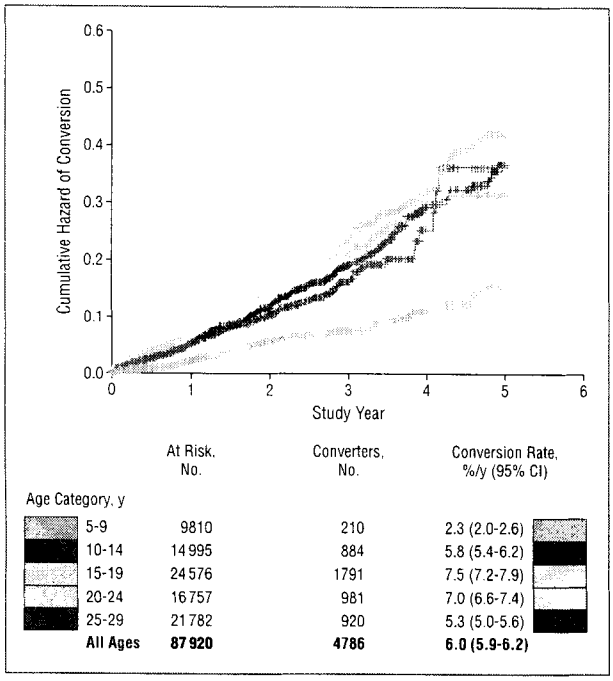
Abbreviation: SSRI, selective serotonin reuptake inhibitor.

*Conversion was defined as a new diagnosis of bipolar disorder as assessed by 2 or more claims. Because of rounding, not all percentages total 100. Psychotropic drug percentages sum to greater than 100 because some patients were prescribed more than 1 class of drug.

†*P* values for the comparison between converters and nonconverters were calculated using χ^2 or unpaired *t* tests for categorical or continuous variables, respectively.

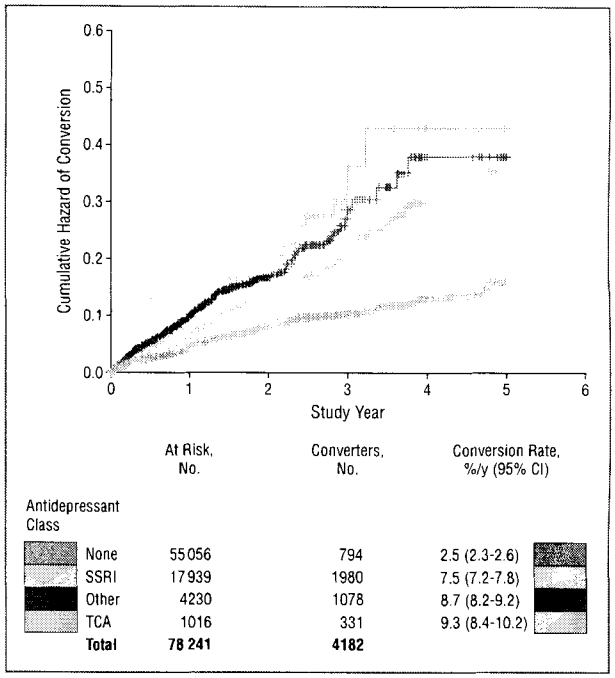
There were clear differences in age composition between converters and nonconverters. In unadjusted analyses, and as depicted in Kaplan-Meier curves, converters were most likely to belong to the 15- to 19-year-old age category and least likely to belong to the youngest group (rate ratio, 3.2; 95% CI, 3.1-3.4) (**Figure 1**).

The conversion rate among antidepressant-treated patients (7.7% per year) was 3-fold that among unexposed patients (2.5% per year; rate ratio, 3.1; 95% CI, 3.0-3.2). Conversion rates differed by medication type: higher for TCAs and other antidepressants and lower for SSRIs (rate ratios vs the no-antidepressant category: 3.7 and 3.0, respectively) (**Figure 2**). Although the TCA and other antidepressant categories did not differ



Age Category, y	At Risk, No.	Converters, No.	Conversion Rate, %/y (95% CI)
5-9	9810	210	2.3 (2.0-2.6)
10-14	14995	884	5.8 (5.4-6.2)
15-19	24576	1791	7.5 (7.2-7.9)
20-24	16757	981	7.0 (6.6-7.4)
25-29	21782	920	5.3 (5.0-5.6)
All Ages	**87920**	**4786**	**6.0 (5.9-6.2)**

Figure 1. Kaplan-Meier estimates of the cumulative hazard of conversion according to age category at study entry. An outcome event (manic conversion) was defined as a new diagnosis of bipolar disorder as assessed by 2 or more claims. Whenever the outcome was preceded by the introduction of a mood stabilizer (lithium or an antiepileptic drug other than phenytoin), the earlier event was used to mark the conversion date. There was a significant difference in hazard rates across the age groups ($P<.001$, log-rank test). CI indicates confidence interval.



Antidepressant Class	At Risk, No.	Converters, No.	Conversion Rate, %/y (95% CI)
None	55056	794	2.5 (2.3-2.6)
SSRI	17939	1980	7.5 (7.2-7.8)
Other	4230	1078	8.7 (8.2-9.2)
TCA	1016	331	9.3 (8.4-10.2)
Total	**78241**	**4182**	

Figure 2. Kaplan-Meier estimates of the cumulative hazard of conversion according to medication category. An outcome event (manic conversion) was defined as a new diagnosis of bipolar disorder as assessed by 2 or more claims. Whenever the outcome was preceded by the introduction of a mood stabilizer (lithium or an antiepileptic drug other than phenytoin), the earlier event was used to mark the conversion date. There was a significant difference in hazard rates across the antidepressant categories ($P<.001$, log-rank test). Patients taking more than 1 antidepressant agent were excluded from analysis, yielding smaller totals for number at risk and number of converters. CI indicates confidence interval; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

significantly from one another, they were kept separate rather than combined into a single category in subsequent analyses.

Age × medication interactions were first apparent in unadjusted analyses stratified by age category and antidepressant medication exposure (**Figure 3**). The conversion ratio between the antidepressant-exposed and antidepressant-unexposed groups was significantly higher in the younger age group (5- to 14-year-olds; rate ratio, 2.9; 95% CI, 2.8-3.1) than in the older age group (15- to 29-year-olds; rate ratio, 1.4; 95% CI, 1.3-1.5; log-rank test, 160.8; $P<.001$). This difference was largely due to the low conversion rate among the younger patients in the antidepressant-unexposed group.

The effects of age and antidepressant exposure on conversion status were further examined through adjusted models that controlled for confounding variables. In all final time-dependent Cox proportional hazards models, there were no sex differences ($P=.08$), but main effects emerged for the diagnoses of severe and mild depression (hazard ratios compared with the anxiety group: 3.4 and 1.3, respectively) and for inpatient status, number of diagnoses, and number of different medications (hazard ratios: 6.7, 1.5, and 1.1, respectively; $P<.001$ for all except where noted otherwise). In parallel to results from the unadjusted analyses, main effects of medication use were highest for TCAs (hazard ratio, 3.9; $P=.002$), followed by other antidepressants (hazard ratio, 3.8) and SSRIs (hazard ratio, 2.1) (**Table 2**, model IVa). Although in all models there was a main effect of age (hazard ratio, 1.1 for each 5-year increase) that was consistent with the unadjusted analyses, several age × medication interactions were also apparent (Table 2, models IIIa-IVb).

Significant negative interactions for age on conversion hazards emerged for the pooled antidepressant, SSRI, and other categories ($\beta=-.05$; $P<.001$ for all). Within each group, age was inversely related to conversion hazards, reaching maximum values in the 10- to 14-year-old category. In contrast, age effects were not apparent in the adjusted analyses for the TCA group at either stratum-specific or overall age levels. The effect of age on conversion status was also seen in the medication- and age-stratified calculations of NNHs (**Table 3**). To assess the risks of antidepressant-associated manic conversion on the least vulnerable patients, we repeated these analyses using only individuals with diagnoses in either the "mild depression" or "anxiety disorders" clusters. In these analyses, values for 5- to 14-year-olds remained at low levels for SSRIs (NNH, 13; 95% CI, 11-15) and the other antidepressants (NNH, 10; 95% CI, 8-11).

COMMENT

This study revealed that age is an effect modifier on antidepressant-associated manic conversion. Specifically, after adjusting for potential confounders, there was an inverse relationship between age and relative hazards of conversion. The hazard was highest for the peripubertal group of 10- to 14-year-old patients, such that treating as

few as 10 (95% CI, 9-12) children with an antidepressant agent could result in at least 1 conversion event, compared with 23 (95% CI, 21-25) among 15- to 29-year-olds.

Our findings are consistent with earlier, although far from definitive, studies describing differential liability to manic induction according to antidepressant class (typically highest for TCAs, lowest for bupropion hydrochloride).[6,32] They are also in keeping with studies documenting a peak age at onset of bipolar disorder of 15 to 19 years in recent cohorts,[33] and younger age at first treatment as a predictor of vulnerability to antidepressant-induced cycle acceleration.[11] Given that hazard rates in this study peaked in the next younger age group (10- to 14-year-olds), our findings suggest that peripubertal children may be especially vulnerable to antidepressant-associated conversion.

Also consistent with our findings, there is an emerging preclinical body of literature that suggests differing vulnerability to the adverse effects of antidepressants according to the developmental stage during which exposure occurs. For example, rodents administered SSRIs prepubertally develop an increased density of serotonin transporters in the frontal cortex that persists into adulthood,[34] and their prepubertal (as opposed to adult) response to serotonergic and noradrenergic probes is dramatically different.[35,36]

In light of this evidence, lack of information regarding pubertal status limited our study. A further limitation was its reliance on administrative rather than clinical data, especially around diagnostic classification and the definition of switching, a shortcoming inherent to other studies that rely on secondary analyses to secure large sample sizes. Other limitations include lack of random assignment in this large sample of convenience, no information on medication compliance, and the potential for confounding by indication, that is, depressed children who are more likely to "naturally" become manic are also those more likely to be prescribed antidepressant drugs. Perhaps the largest limitation and potential threat to the study's validity has to do with the fundamental difficulty in disentangling what may be natural progression of the illness from larger secular trends (such as the more pervasive use of antidepressants and mood stabilizers and of diagnosing bipolar disorder, especially among youths) from true induction of constitutionally vulnerable individuals by means of a pharmacologic "irritant."

Although we cannot entirely rule out the role of these underlying secular trends on our results, the fact that on average subjects were followed for less than 1 year suggests that such effects were probably small. Furthermore, we introduced a variety of measures into our analyses to adjust for confounding, particularly of illness severity, given that the earlier the age at onset, the more severe the illness course is likely to be, and the greater the illness severity, the higher the risk of conversion. Despite these efforts, some residual confounding may well have persisted.

Residual confounding and sample size considerations may explain the lack of a clear conversion age effect for TCAs, in contrast to SSRIs and other antidepressants. Alternatively, the lack of TCA effect modification may not be an artifact. It has been demonstrated that TCAs are no better than placebo in the treatment of depression in children and adolescents,[37,38] a negative finding not likely due to failed studies, given an adequately powered recent study.[39] Preclinical studies with nonhuman primates have shown different timelines in the maturation of central nervous system pathways, with adult patterns of serotonergic innervation reached by childhood[40] as opposed to noradrenergic and dopaminergic pathways, which continue to develop through puberty[41] and well into young adulthood.[42] Given that most TCAs have predominant effects on adrenergic pathways, the unavailability of a fully mature neural substrate on which to act may explain their lack of efficacy—or of heightened liability to behavioral toxicity—among children and adolescents.

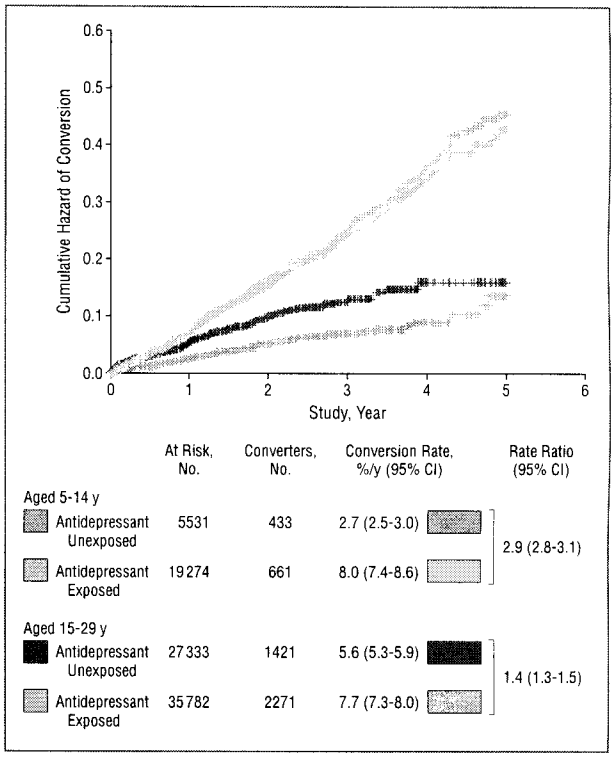


Figure 3. Kaplan-Meier estimates of the cumulative hazard of conversion according to age category and antidepressant exposure. An outcome event (manic conversion) was defined as a new diagnosis of bipolar disorder as assessed by 2 or more claims. Whenever the outcome was preceded by the introduction of a mood stabilizer (lithium or an antiepileptic drug other than phenytoin), the earlier event was used to mark the conversion date. There were significant differences in hazard rates (1) across the antidepressant-exposed and antidepressant-unexposed categories; (2) among the antidepressant-unexposed group, across those younger than 14 years/older than 15 years; and (3) across the 4 categories ($P<.001$, log-rank test for each comparison). CI indicates confidence interval.

The large sample size of our study allowed us to investigate the effects of age on antidepressant-associated manic conversion and revealed strong age × medication interactions. Children and adolescents younger than 15 years, especially those treated with SSRIs or other antidepressants, are at heightened risk of manic conversion, cautions to be evaluated clinically, scientifically, and ethically[43] in the context of a growing evidence base for their use.[39,44-46] Further pharmacoepidemiologic, pharmacovigilance, and long-term prospective studies are needed

Table 2. Adjusted Hazard Ratios (HRs) for Manic Conversion: Effects of Age Group, Antidepressant (AD) Category, and Their Interactions (4786 Converters)*

	Main Effects Only				Main Effects and Interactions			
	Models Ia and Ib		Models IIa and IIb		Models IIIa and IIIb		Models IVa and IVb	
Hierarchical Models†	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Model Ia								
Age (per 5-y increment)	1.2 (1.1-1.2)	<.001						
Model Ib								
Age group, y								
5-9	0.5 (0.4-0.6)	<.001						
10-14	1.0 (0.9-1.1)	.90						
15-19	1.2 (1.1-1.3)	<.001						
20-24	1.2 (1.1-1.3)	<.001						
25-29	1 (Reference category)							
Model IIa								
Any AD (n = 2932 exposed)			1.8 (1.3-2.6)	<.001				
Model IIb								
AD category								
SSRI (n = 2329)			1.2 (1.1-1.2)	<.001				
Other AD (n = 1268)			1.5 (1.3-1.7)	<.001				
Tricyclic AD (n = 389)			2.0 (1.6-2.4)	<.001				
Model IIIa								
Any AD × age								
Any AD					2.3 (1.8-2.8)	<.001		
AD × age					*(−0.05) 55.5*	<.001		
Model IIIb								
Any AD × age group								
AD × 5-9 (n = 109)					1.5 (1.2-1.9)	<.001		
AD × age 10-14 (n = 552)					1.8 (1.5-2.1)	<.001		
AD × age 15-19 (n = 1093)					1.5 (1.3-1.7)	<.001		
AD × age 20-24 (n = 591)					1.2 (1.1-1.4)	<.001		
AD × age 25-29 (n = 587)					1 (Reference category)			
Model IVa								
AD category × age								
SSRI							2.1 (1.5-3.1)	<.001
SSRI × age							*(−0.05) 64.5*	<.001
Other AD							3.8 (2.0-7.1)	<.001
Other AD × age							*(−0.05) 22.4*	<.001
Tricyclic AD							3.9 (1.4-11.0)	.002
Tricyclic AD × age							*(−0.02) 1.3*	.25
Model IVb								
AD category × age group, y								
SSRI × age 5-9 (n = 86)							2.2 (1.6-3.2)	<.001
SSRI × age 10-14 (n = 458)							2.4 (1.9-2.9)	<.001
SSRI × age 15-19 (n = 879)							1.8 (1.5-2.1)	<.001
SSRI × age 20-24 (n = 460)							1.4 (1.2-1.7)	<.001
SSRI × age 25-29 (n = 446)							1 (Reference category)	
Other AD age 5-9 (n = 34)							2.0 (0.7-5.6)	.17
Other AD age 10-14 (n = 210)							2.2 (1.5-3.1)	<.001
Other AD age 15-19 (n = 484)							1.8 (1.4-2.3)	<.001
Other AD age 20-24 (n = 262)							1.4 (1.04-1.8)	.03
Other AD age 25-29 (n = 278)							1 (Reference category)	
Tricyclic AD × age 5-9 (n = 20)							1.4 (0.6-3.1)	.43
Tricyclic AD × age 10-14 (n = 66)							1.7 (0.95-3.1)	.07
Tricyclic AD × age 15-19 (n = 127)							1.4 (0.8-2.4)	.24
Tricyclic AD × age 20-24 (n = 74)							1.6 (0.9-2.9)	.11
Tricyclic AD × age 25-29 (n = 102)							1 (Reference category)	

Abbreviations: CI, confidence interval; SSRI, selective serotonin reuptake inhibitor.

*Hazard ratios were calculated with the final time-dependent Cox proportional hazards model and are adjusted for sex, diagnosis, number of mental health diagnoses, other antidepressant use, overall number of psychotropic medications used, and inpatient hospitalization status. For models with any given $x \times y$ interaction term, the main effect terms x and y are also included.

†Models I and II include main effects only; models III and IV, main effects and their interactions. Data are presented as (β coefficients) χ^2 values for the interaction terms of models IIIa and IVa; the interactions are then deconstructed in models IIIb and IVb, respectively.

Table 3. Number Needed to Harm (NNH), by Antidepressant Class and Age Category*

Age, y	Converters, No. (%) Not Exposed	Exposed	NNH (95% CI)
Any Antidepressant			
All ages	1854 (3.4)	2932 (8.9)	18 (16-20)
5-9	101 (1.2)	109 (9.1)	13 (11-14)
10-14	332 (3.1)	552 (12.7)	10 (9-12)
15-19	698 (4.8)	1093 (10.9)	16 (15-18)
20-24	390 (4.3)	591 (7.6)	31 (29-33)
25-29	333 (2.7)	587 (6.2)	29 (27-31)
15-29	1421 (4.1)	2271 (8.3)	23 (21-25)
Selective Serotonin Reuptake Inhibitors			
All ages	2457 (4.0)	2329 (8.8)	21 (19-23)
5-9	124 (1.4)	86 (9.6)	12 (11-14)
10-14	426 (3.7)	458 (13.1)	11 (9-12)
15-19	912 (5.6)	879 (10.7)	20 (18-21)
20-24	521 (5.0)	460 (7.3)	43 (41-45)
25-29	474 (3.3)	446 (5.9)	39 (37-41)
Other Antidepressants			
All ages	3518 (4.6)	1268 (11.4)	15 (13-16)
5-9	176 (1.8)	34 (11.9)	10 (8-11)
10-14	574 (4.9)	210 (15.8)	9 (8-11)
15-19	1307 (6.2)	484 (13.9)	13 (12-14)
20-24	719 (5.1)	262 (9.8)	21 (20-23)
25-29	642 (3.5)	278 (8.2)	21 (19-23)
Tricyclic Antidepressants			
All ages	4397 (5.2)	389 (12.9)	13 (12-14)
5-9	190 (2.0)	20 (8.2)	16 (14-18)
10-14	818 (5.0)	66 (13.0)	14 (12-15)
15-19	1664 (7.0)	127 (16.3)	11 (10-12)
20-24	907 (5.6)	74 (12.7)	14 (13-15)
25-29	818 (5.9)	102 (11.2)	14 (12-15)

*Abbreviation: CI, confidence interval.
†Values were calculated using the formulas of Sackett et al,[36] and are rounded to the nearest integer.

to confirm our findings and to establish the long-term safety profile of these drugs.[47] Our findings must be considered preliminary associations and must not be taken to equate direct causality, especially in light of the limitations we outlined earlier. Despite this important caveat, judicious prescription practices and thorough risk-benefit analysis at the level of the individual patient are warranted for the age-specific use of antidepressant agents. Caution and restraint may be especially pertinent when treating children whose symptoms are not a major source of impairment, those with a strong family history of bipolar disorder, or those who have not yet tried (and failed) psychotherapeutic interventions of proven efficacy.[48-51]

Accepted for publication April 8, 2004.

This study was supported in part by Scientist Career Development Award 01792 from the National Institute of Mental Health, Rockville, Md.

We acknowledge the statistical consultation provided by Ralitza Gueorguieva, PhD.

Correspondence: Andres Martin, MD, MPH, Child Study Center, Yale University School of Medicine, 230 S Frontage Rd, New Haven, CT 06520-7900 (Andres.Martin@Yale.Edu).

What This Study Adds

- It has long been known that antidepressant medications can precipitate mania in vulnerable individuals, but little is known about the effects of age on this clinical phenomenon.
- Differing response and adverse effect profiles according to developmental stage have been clinically described for antidepressant medications, and a preclinical body of literature suggests that the prepubertal (as opposed to the adult) response to serotonergic and noradrenergic probes can dramatically differ from each other.
- This study replicates earlier (although still inconclusive) findings that antidepressant drug therapy can induce manic conversion among vulnerable individuals and that antidepressant categories differ in their manic induction propensities (highest for TCAs and the other antidepressants and lowest for SSRIs).
- To the best of our knowledge, this is the first study to specifically address age effects on antidepressant-induced mania. Significant inverse effects between age and manic induction were found for SSRIs and other antidepressants but not for TCAs.
- Peripubertal children were found to be at highest risk for conversion (NNH: 10 [95% CI, 9-12] among 10- to 14-year-olds vs 23 [95% CI, 21-25] among 15- to 29-year-olds).
- Until clinical and prospective studies confirm or refute these findings, judicious prescription practices may be especially pertinent when treating children whose symptoms are not a major source of impairment, those with a strong family history of bipolar disorder, or those who have not yet tried (and failed) psychotherapeutic interventions of proven efficacy.

REFERENCES

1. Kline NS. Clinical experience with iproniazid (Marsilid). *J Clin Exp Psychopathol.* 1958;19(supp 1):72-79.
2. Lewis JL, Winokur G. The induction of mania: a natural history study with controls. *Arch Gen Psychiatry.* 1982;39:303-306.
3. Bunney WE Jr, Murphy DL, Goodwin FK, Borge GF. The "switch process" in manic-depressive illness, I: a systematic study of sequential behavioral changes. *Arch Gen Psychiatry.* 1972;27:295-302.
4. Bunney WE Jr. Drug therapy and psychobiological research advances in the psychoses in the past decade. *Am J Psychiatry.* 1978;135(suppl):8-13.
5. Prien RF, Kupfer DJ, Mansky PA, et al. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate–imipramine combination. *Arch Gen Psychiatry.* 1984;41:1096-1104.
6. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. *Br J Psychiatry.* 1994;164:549-550.
7. Fava GA. Can long-term treatment with antidepressant drugs worsen the course of depression? *J Clin Psychiatry.* 2003;64:123-133.
8. Boerlin HL, Gitlin MJ, Zoellner LA, Hammen CL. Bipolar depression and antidepressant-induced mania: a naturalistic study. *J Clin Psychiatry.* 1998;59:374-379.
9. Angst J. Switch from depression to mania: a record study over decades between 1920 and 1982. *Psychopathology.* 1985;18:140-154.
10. Kukopulos A, Caliari B, Tundo A, et al. Rapid cyclers, temperament, and antidepressants. *Compr Psychiatry.* 1983;24:249-258.
11. Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L. Antidepressant-induced mania and cycle acceleration: a controversy revisited. *Am J Psychiatry.* 1995;152:1130-1138.
12. Post RM, Altshuler LL, Frye MA, et al. Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers. *Bipolar Disord.* 2001;3:259-265.
13. Maj M, Pirozzi R, Magliano L, Bartoli L. The prognostic significance of "switch-

ing" in patients with bipolar disorder: a 10-year prospective follow-up study. *Am J Psychiatry*. 2002;159:1711-1717.
14. Coryell W, Solomon D, Turvey C, et al. The long-term course of rapid-cycling bipolar disorder. *Arch Gen Psychiatry*. 2003;60:914-920.
15. Rushton JL, Whitmire JT. Pediatric stimulant and selective serotonin reuptake inhibitor prescription trends: 1992 to 1998. *Arch Pediatr Adolesc Med*. 2001; 155:560-565.
16. Zito JM, Safer DJ, DosReis S, et al. Rising prevalence of antidepressants among US youths. *Pediatrics*. 2002;109:721-727.
17. Zito JM, Safer DJ, DosReis S, et al. Psychotropic practice patterns for youth: a 10-year perspective. *Arch Pediatr Adolesc Med*. 2003;157:17-25.
18. Zito JM, Safer DJ, dosReis S, Gardner JF, Boles M, Lynch F. Trends in the prescribing of psychotropic medications to preschoolers. *JAMA*. 2000;283:1025-1030.
19. Costello EJ, Pine DS, Hammen C, et al. Development and natural history of mood disorders. *Biol Psychiatry*. 2002;52:529-542.
20. Jensen PS, Bhatara VS, Vitiello B, Hoagwood K, Feil M, Burke LB. Psychoactive medication prescribing practices for US children: gaps between research and clinical practice. *J Am Acad Child Adolesc Psychiatry*. 1999;38:557-565.
21. Connor DF, Brent DA, Riddle MA. Paroxetine and the FDA. *J Am Acad Child Adolesc Psychiatry*. 2004;43:127-130.
22. Brent DA, Birmaher B. British warnings on SSRIs questioned. *J Am Acad Child Adolesc Psychiatry*. 2004;43:379-380.
23. Varley CK. Psychopharmacological treatment of major depressive disorder in children and adolescents. *JAMA*. 2003;290:1091-1093.
24. Martin A, Leslie D. Psychiatric inpatient, outpatient, and medication utilization and costs among privately insured youths, 1997-2000. *Am J Psychiatry*. 2003; 160:757-764.
25. Martin A, Leslie D. Trends in psychotropic medication costs for children and adolescents, 1997-2000. *Arch Pediatr Adolesc Med*. 2003;157:997-1004.
26. Simon GE, Unutzer J, Young BE, Pincus HA. Large medical databases, population-based research, and patient confidentiality. *Am J Psychiatry*. 2000;157:1731-1737.
27. *International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*. Geneva, Switzerland: World Health Organization; 1997.
28. Wilens TE, Biederman J, Kwon A, et al. A systematic chart review of the nature of psychiatric adverse events in children and adolescents treated with selective serotonin reuptake inhibitors. *J Child Adolesc Psychopharmacol*. 2003;13:143-152.
29. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 1998.
30. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EBM*. Edinburgh, Scotland: Churchill Livingstone; 2000.
31. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York: Springer-Verlag NY Inc; 2000.
32. Bottlender R, Rudolf D, Strauss A, Moller HJ. Mood-stabilisers reduce the risk of developing antidepressant-induced manifom states in acute treatment of bipolar I depressed patients. *J Affect Disord*. 2001;63:79-83.
33. Chengappa KN, Kupfer DJ, Frank E, et al. Relationship of birth cohort and early age at onset of illness in a bipolar disorder case registry. *Am J Psychiatry*. 2003; 160:1636-1642.
34. Wegerer V, Moll GH, Bagli M, Rothenberger A, Ruther E, Huether G. Persistently increased density of serotonin transporters in the frontal cortex of rats treated with fluoxetine during early juvenile life. *J Child Adolesc Psychopharmacol*. 1999; 9:13-24.
35. Carrey NJ, Dursun S, Clements R, Renton K, Waschbusch D, MacMaster FP. Noradrenergic and serotonergic neuroendocrine responses in prepubertal, peripubertal, and postpubertal rats pretreated with desipramine and sertraline. *J Am Acad Child Adolesc Psychiatry*. 2002;41:999-1006.
36. Leckman JF, Young C. Commentary: noradrenergic and serotonergic neuroendocrine responses in prepubertal, peripubertal, and postpubertal rats pretreated with desipramine and sertraline. *J Am Acad Child Adolesc Psychiatry*. 2002;41: 1007-1009.
37. Hazell P, O'Connell D, Heathcote D, Robertson J, Henry D. Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis. *BMJ*. 1995; 310:897-901.
38. Kaufman J, Martin A, King RA, Charney DS. Are child-, adolescent- and adult-onset depression one and the same disorder? *Biol Psychiatry*. 2001;49:980-1001.
39. Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40:762-772.
40. Goldman-Rakic PS, Brown RM. Postnatal development of monoamine content and synthesis in the cerebral cortex of rhesus monkeys. *Brain Res*. 1982;256: 339-349.
41. Woo TU, Pucak ML, Kye CH, Matus CV, Lewis DA. Peripubertal refinement of the intrinsic and associational circuitry in monkey prefrontal cortex. *Neuroscience*. 1997;80:1149-1158.
42. Rosenberg DR, Lewis DA. Postnatal maturation of the dopaminergic innervation of monkey prefrontal and motor cortices: a tyrosine hydroxylase immunohistochemical analysis. *J Comp Neurol*. 1995;358:383-400.
43. Vitiello B, Jensen PS, Hoagwood K. Integrating science and ethics in child and adolescent psychiatry research. *Biol Psychiatry*. 1999;46:1044-1049.
44. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*. 1997;54:1031-1037.
45. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41:1205-1215.
46. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *JAMA*. 2003;290:1033-1041.
47. Greenhill LL, Vitiello B, Abikoff H, et al. Developing methodologies for monitoring long-term safety of psychotropic medications in children: report on the NIMH conference, September 25, 2000. *J Am Acad Child Adolesc Psychiatry*. 2003; 42:651-655.
48. Asarnow JR, Jaycox LH, Tompson MC. Depression in youth: psychosocial interventions. *J Clin Child Psychol*. 2001;30:33-47.
49. Harrington R, Whittaker J, Shoebridge P, Campbell F. Systematic review of efficacy of cognitive behaviour therapies in childhood and adolescent depressive disorder. *BMJ*. 1998;316:1559-1563.
50. Mufson L, Weissman MM, Moreau D, Garfinkel R. Efficacy of interpersonal psychotherapy for depressed adolescents. *Arch Gen Psychiatry*. 1999;56:573-579.
51. Ollendick TH, King NJ. Empirically supported treatments for children with phobic and anxiety disorders: current status. *J Clin Child Psychol*. 1998;27:156-167.