

Impacts of new safety information: The case of pediatric antidepressant use and suicidality

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Characterizing declines in pediatric antidepressant use after new risk disclosures

ABSTRACT

Steep declines in pediatric antidepressant use were documented following the 2004 release of new safety information associating antidepressants with a risk of suicidality. We examine whether declines in pediatric antidepressant use were steeper among individuals with certain clinical or family characteristics. We find that declines in antidepressant use were associated with new (as compared to ongoing) treatment episodes. Also, although rates of antidepressant use were higher among children of college educated parents prior to risk disclosures, these children were significantly more likely to forgo antidepressant medication than children of less educated parents after risk disclosures. We did not find differences by child's psychiatric impairment status or one measure of parent risk aversion. Understanding the variation in responses to medication risk disclosure by children's clinical and family characteristics may be helpful to providers in tailoring discussions with patients and to regulators in anticipating the consequences of future risk warnings.

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Risk disclosures regarding pharmaceutical treatments have become more common in recent years (Hartman, 2009), and are likely to increase if the FDA successfully implements a ‘Sentinel’ system to identify adverse drug events as planned (Avorn & Schneeweiss, 2009). Yet, little is known about how the release of new risk information affects treatment choices for individuals. Providers may adopt an across-the-board change in their practice style, forgoing suspected medications altogether, they may carefully consider the risks and benefits for each patient before choosing whether and which medication to use, or they may respond to individual patient preferences regarding concern about new risk disclosures. A better understanding of whether patients’ clinical and family characteristics affect treatment choice after safety warnings may help providers tailor their communication with patients and aid regulators in anticipating the range of likely responses by the public. We examine one case study – the release of new information about pediatric antidepressant use and suicidality risk – to better understand who is affected by new safety information.

New information surfaced in mid 2003 regarding a possible association between pediatric antidepressant use and suicidality risk. After further investigation, available evidence from the Food and Drug Administration (FDA) suggested there were possible risks associated with pediatric antidepressant use. The evidence on risks came from a meta-analysis of clinical trial data, and indicated an increased risk of suicidality in pediatric patients on antidepressants (2% in placebo versus 4% in drug arms). It is important to emphasize this evidence related to suicidality -- no trial participant committed suicide.

In response to these risks, the FDA issued several public health advisories, and made the decision to add a black box warning (BBW) to antidepressant packaging in October 2004. This was the most serious action the FDA could take short of banning pediatric antidepressant use.

Media coverage of this risk disclosure was extensive, and research suggests that the media coverage overemphasized the suicidality risk compared to risks associated with untreated depression (Barry & Busch, 2009).

In response to this new risk information, several research studies have found that sharp declines in pediatric antidepressant use occurred, suggesting an increase in the undertreatment of an already undertreated disease (Busch & Barry, 2009; Gibbons et al, 2007; Harris, 2004; Libby et al. 2007; Nemeroff et al. 2007; Olfson, Marcus & Druss, 2008; Rosack, 2005). Against this backdrop, and following a decade of steady reductions in youth suicide, an unexpected increase in national youth suicide rates led to speculation that the decline in antidepressant use may have played a role (Bridge, Greenhouse & Weldon, 2008). Although a causal association could not be established and other hypotheses, such as changes in youth access to firearms, the prevalence of alcohol use, or web-based social networks were posited, the coinciding trends of reductions in pediatric antidepressant use and increasing youth suicide rates raised public health concerns about the possible unintended consequences of the FDA advisories.

New Contribution

This study goes beyond previous work by examining whether clinical and family characteristics are associated with differential declines in pediatric antidepressant medication use following this risk disclosure. Specifically, we examine whether there was a differential decline in antidepressant use among new versus experienced pediatric antidepressant users, by the degree of a child's impairment, by children with more versus less educated parents, and by children of risk averse parents.

To our knowledge, all prior work in this area has relied on pharmacy or outpatient claims data and examines a limited subset of the population (i.e., privately insured, enrollees of a single health plan). In contrast, we use the Medical Expenditure Panel Survey (MEPS) to examine pediatric antidepressant use from 2002 through 2006. The advantage of this survey data is that more detailed information on child and parent characteristics is available, both on treated and untreated children. A second strength is that these data are from a national sample, allowing us to make national estimates of declines in pediatric antidepressant use. This information can help regulators, providers and health plans anticipate the effects of future risk disclosures, as well as provide information on how new health information is diffused more generally.

Potential Determinants of Child Antidepressant Use

We expected that patients and providers decide whether to use antidepressant medication as treatment for children based on clinical characteristics and family preferences. First, we examined whether reduced utilization was due to fewer children being started on antidepressants, as compared to previously treated children stopping medication. We hypothesized that declines would be among the former group because the risk of suicidality has been estimated to be highest during the first month after starting antidepressants, and especially during the first four weeks (Jick, Kaye & Jick, 2004; Brent et al., 2009), and that known risk information, including that in the meta-analysis presented at an FDA advisory meeting, is based on clinical trial data of typically under twelve weeks' duration (Hammad, Laughren & Racoosin, 2006). Second, we explored the severity of symptoms in children forgoing antidepressants after safety warnings. Clinical trial evidence on the efficacy of SSRIs in children is limited to children with specific clinical symptoms (e.g., DSM-IV diagnosis of major depressive disorder (MDD) or Children's

Depression Rating Scale-Revised score of 45 or higher). If reductions in antidepressant use were concentrated among children with less severe symptoms, the potential health impact of untreated depression would be less than if declines occurred primarily among children with greater psychiatric impairment.

We also examined whether parent characteristics play a role in how FDA safety warnings were interpreted. Prior research has suggested that more educated individuals adopt new medical technology more quickly than others (Glied & Lleras-Muney, 2003; Rosenzweig & Schultz, 1989). College-educated parents may have greater exposure or access to scientific information about drug risks, and may be more likely to make treatment decisions on the basis of this information than other parents. Conversely, more educated parents, with a heightened awareness of the effects of untreated depression on long-term outcomes, may be more reticent to forgo medication for their child. Results from this analysis can inform models of the education-health gradient and improve our understanding of the effect of education on treatment choice.

We also considered parent risk aversion as a possible source of differential utilization, based on research indicating that individuals tend to overestimate small risks (Kanheman & Tversky, 1979). We hypothesized that if parent attitudes toward risk factor into treatment decisions, risk averse parents would be more likely to seek treatment for their children using antidepressants before the warning. However, after the warning, we would expect that more risk averse parents would opt against treating their children's depression with antidepressants, perhaps making treatment decisions on the basis of relatively low probability safety risks.

Study Data and Methods

We used the MEPS, an ongoing nationally representative panel survey of the U.S. civilian non-institutionalized population, with approximately 17,000 individuals in each cohort. A household remains in the panel for two and a half years, and is surveyed five times over that period. During each round, household respondents are asked to record all health care utilization, including prescribed medication, since the prior round. For families reporting prescription drug use, pharmacies identified by the household were contacted to identify the date a prescription was filled, national drug code (NDC), medication name, strength (amount and unit), and quantity (package size and amount dispensed). Once each year, adult household members complete a written questionnaire. We limited our sample to children, adolescents and young adults ages 5 to 21, excluding individuals without information for all survey rounds or not in their household for the entire calendar year.

Measures

Antidepressant use. We created three variables reflecting each subject's antidepressant use, based on use of any of the 36 drugs mentioned in the FDA BBW (see Table 1). First, we created a dichotomous variable indicating whether the subject filled a prescription for any antidepressant during the calendar year. Next, the first time an individual reported using a prescription drug, they were asked 'When was the first year you took this drug?' We used this variable to categorize antidepressant users into two distinct groups: new users (those whose first experience using an antidepressant drug was in the current year) and experienced users. The latter group included individuals in the midst of a treatment episode that began in the prior year, as well as individuals beginning a new treatment episode but who had previously used an

antidepressant. Given the organization of the MEPS dataset, we were not able to differentiate these two types of experienced users.

Mental health impairment. The MEPS includes the Columbia Impairment Scale (CIS), a 13-item global measure of impairment administered to parents by a lay interviewer. Four areas of functioning are addressed: interpersonal relations, broad psychopathological domains, functioning in job or school, and use of leisure time. Items are scored on a range of 0 to 4, with total scores ranging from 0 to 52. We note that because this measure is parent report, it is possible that some aspects of the child's mental health and functioning may be misreported, although a study by Bird et al. (1996) found that, when administered to parents (as in the MEPS), the CIS correlates with the clinicians' Children's Global Assessment Scale (CGAS) score ($r = -.58$). We used the cutoff score of ≥ 16 established by Bird and colleagues to indicate more severe psychiatric impairment. This measure was only available for subjects ages 5-17, so we limited analyses including this variable to children within this age range.

Parents' education. We created a dichotomous variable indicating whether either the child's mother or father had a bachelor's degree or higher at the time of the survey. We limited analyses using this variable to children in the 5-17 age range since treatment decisions for those ages 18-21 are less likely to be determined by a parent.

Parents' risk aversion. Each adult in the MEPS was asked in a written survey once each year whether they agreed or disagreed with the following statement: I'm more likely to take risks than the average person. Responses were on a Likert scale and included: disagree strongly, disagree somewhat, uncertain, agree somewhat, agree strongly. To categorize parents' aversion to risk, we created a variable equal to one when either the mother or father disagreed strongly with this statement, and zero otherwise. Fifty percent of children had at least one parent who

was 'risk averse' in this sample. Again, we limited analyses using this variable to children in the 5-17 age range since the level of a parent's risk aversion is less likely to affect treatment decisions for those ages 18-21.

Other independent variables. Our model also included three age categories (age 5-9; 10-13; or 14-18), gender, whether the child had private insurance, public insurance or was uninsured, whether the child's family was low income (defined as <200% the federally defined poverty level), and whether the child's race was black, white, or other.

Estimation Strategy

We used weighted logistic regression to estimate utilization trends by degree of child's psychiatric impairment, parent's education, and parents' attitude toward risk. We stacked the four calendar years, and included year dummies and interacted each of these characteristics with the years of our study, controlling for the other independent variables noted above. To determine the effects on the original scale, we used the method of recycled predictions, calculating the adjusted probability of the relevant outcome for each individual in our sample, assuming the individual was treated in each of the relevant time periods (Kleinman & Norton, 2009). In all estimates, we adjust for the complex sampling strategy used in the MEPS, including the estimation weight, sampling strata, and primary sampling unit (Machlin, Yu & Zodet, 2005).

Prior studies had found steady increases in pediatric antidepressant use in the period prior to risk disclosures (Libby, Brent & Morrato, 2007). Generally, these studies estimated the impact of the new risk information by subtracting actual utilization rates from the predicted level, assuming that upward utilization trends would continue. We instead test whether utilization rates in each year of our data are statistically significantly different from 2003

utilization rates. This produced a more conservative estimate of the number of untreated children following safety warnings.

Study Results

Because the MEPS is a national sample, we find few differences in demographic characteristics across time periods. The unadjusted 12-month prevalence rates of antidepressant use in the pre- and post-risk disclosure periods are presented in Table 2, Row 1. Table 2, rows 2 and 3 shows the unadjusted changes in antidepressant use, stratified by experienced or new user status. Overall antidepressant use declined from 2.91% to 2.16%, a 26% reduction, with about 500,000 fewer individuals treated with antidepressants. The entire decline occurred among new antidepressant users, with rates going from 1.65% to 0.87%, representing a 47% reduction. We observed no decline among experienced users. Because the decline in antidepressant use was solely among new users, we focused on this group in the analyses that follow.

We next examined whether there were differential declines in new antidepressant use by impairment score ($CIS \geq 16$). To aid interpretation of the magnitude of effects, we show the adjusted probability of new antidepressant use by impairment in Figure 1. Antidepressant use declined substantially in the post risk disclosure period in both groups, with no significant differential decline by impairment status by 2005, although the decline started earlier in the no impairment group (in 2004 versus 2005). For the no impairment group, use declined from 0.9% in 2003 to 0.3% in 2004. Although these rates were low, given that most individuals in the population had no impairment, this group reflects approximately half of those individuals using antidepressants. As expected, children and adolescents with impairment ($CIS \geq 16$) were more

likely to use an antidepressant compared with those without, and declines were also seen in this group: antidepressant use went from 5.7% in 2003 to 3.2% in 2005.

Figure 2, Panel A indicates results examining whether there were differential declines in new antidepressant use after risk disclosure by parent education level. While both groups showed lower use of antidepressants, children and adolescents of more educated parents had significantly larger declines in antidepressant use in after risk disclosures. We found that in 2003, 1.8% of children whose parents had a college degree were new users of antidepressants, compared with 1.3% of children whose parents did not have a college degree, a 28% difference. Antidepressant use declined to 0.6% for children of college educated parents, and to 1.1% for children whose parents did not have a college degree by 2004 . The decline for children of more educated parents was so steep that in 2004, these children had lower rates of new antidepressant use than children of less educated parents. In a robustness check, we find qualitatively similar results when reclassifying education as three levels (i.e., no high school/GED; high school graduate; some college).

Figure 2, Panel B indicates changes in new antidepressant use after risk disclosure by parental risk aversion. Children of risk averse parents were more likely to be new antidepressant users prior to risk disclosure. We found that children of risk averse parents significantly reduced their antidepressant use (from 1.8 to 1.0 percent of population), but there was no significant differential decline in antidepressant use by parent's risk aversion.

Discussion

Confirming prior research, we found that the use of antidepressant medications among children, adolescents and young adults declined significantly between 2002 and 2006, with over

half a million fewer individuals treated each calendar year. Declines in antidepressant use were almost entirely attributable to fewer newly treated individuals. This finding suggests that the main impact of the risk disclosures may have been in reducing the initiation of antidepressant medications, rather than in fostering their discontinuation. There are at least two possible explanations for this finding. First, concerns over increased suicidal ideation associated with antidepressant use are based on clinical trials of relatively short duration, with very limited data on longer term and maintenance antidepressant treatment. Thus, suicidality associated with antidepressants is mostly perceived as an acute, early-treatment-emergent consideration. Second, when deciding whether to use an antidepressant, individuals must weigh risks and benefits. For new users, whether their symptoms will respond to medication is unknown. For experienced users, the patient has more information about their individual benefit from medication use. Individuals in the maintenance phase of treatment may be more likely to benefit from antidepressants.

Regarding psychiatric impairment, we found declines in new antidepressant use in individuals both with and without impairment, suggesting that antidepressant use did not decline differentially based on illness severity. This negative finding needs to be interpreted in the context of the measure's inherent limitations within MEPS. For one, measures of psychiatric impairment were taken at only one point in time, and we were unable to determine impairment status at the moment when the decision was made whether or not to prescribe antidepressants. The fact that so many subjects with no impairment were receiving treatment may be an indication of the efficacy of treatment, or may suggest that milder and less impairing conditions (e.g. adjustment disorders) were also being treated.

Children and adolescents of college educated parents had a more pronounced decline in antidepressant treatment compared with those of less educated parents. With these data, we cannot determine whether this effect is due to differences in the types of providers chosen by more educated parents, or differences in parent decision making. To the extent that these differences are due to differences in parent decision making, that more educated parents may incorporate new information about health care treatments in decision making suggests that clinicians and regulatory agencies should consider new approaches for distributing risk information. While the FDA communicates directly to providers (through letters sent directly to health care professionals), FDA risk warnings are also disseminated to the lay public through the news media. It is important for providers to recognize that their patients have likely been exposed to media coverage, which in some cases may simplify or distort information on levels of risk exposure and scientific uncertainty (Schwarz & Woloshin, 2002; Moynihan, Bero & Ross-Degnan, 2000). Such reports are also more likely to focus on adverse events associated with treatment (e.g. antidepressant-related suicidal ideation), than on risks associated with lack of treatment (e.g. suicide in untreated depression) (Barry & Busch, 2009). Our findings suggest that it is important for providers to consider the education level of patients and their families when discussing treatment alternatives.

Individual biases (i.e., propensity to seek or avoid risks) may also influence individual treatment choices. While we find that treatment rates differ by parent risk aversion, we did not identify a differential decline in antidepressant use by parent risk aversion after risk disclosure. This has important implications for the larger movement in health care toward greater consumerism to the extent that well-known biases in decision-making, such as the tendency to overestimate small risks, may influence treatment choices.

These trends highlight the need for further research on the effects of new risk information and risk warnings on treatment patterns. Our findings provide information on one specific case -- the release of new risk information on pediatric antidepressant use. Whether similar effects would be found for newly identified risks of other treatments is unknown. Responses to safety warnings may differ for treatments not related to mental health disorders or for different populations (e.g., adults, pregnant women). Moreover, the risk in this case concerned a potentially life threatening side effect. Different treatment patterns may emerge in response to disclosure of less severe risks. Also important, to better guide the FDA in future decisions regarding how to convey risk information, more research concerning the mechanism by which new risk information is incorporated into treatment decisions may be important. For example, if the decision to forgo treatment is made primarily by the patient or the family, this suggests that communicating new risk disclosures via the news media and through other venues may be helpful in ensuring that all parents have access to this information. However, if decision making occurs primarily at the physician level, effective communication strategies may differ. Finally, the data presented here reflect treatment patterns through 2006. In future years, there may be rebound effects that result in increased pediatric antidepressant utilization. More information about future rates of pediatric antidepressant treatment will be helpful in assessing the longer term response to this risk disclosure.

Two important strengths of this study compared with prior work in the area are that data are derived from a representative sample, allowing us to consider effects for all children and adolescents, and our capacity to examine individual and family characteristics not available in pharmacy claims data. At the same time, our study has a number of limitations worth noting. First, the sample was relatively small in size, with only about 200 antidepressant users in each

year. Second, we did not examine whether there were changes in the type of provider prescribing medication. Prior research has suggested a shift from antidepressant treatment provided in primary care to specialty care post FDA warnings. Due to difficulty assigning individual prescriptions to a specific provider type in the MEPS, we did not examine this issue. Third, we did not consider individual diagnoses. Diagnosis codes provided in the MEPS are derived from parent report of the child's symptoms or reasons for individual visits. We did not think this diagnostic data would be reliable for our purposes, so elected not to include this variable. Finally, because the data in MEPS was self-reported, treatment rates may be undercounted. However, this potential bias is not likely to differ over time.

Despite these limitations, our findings may help clinicians tailor their communication of antidepressant risks and benefits to patients and their families, especially when considering whether to initiate antidepressant treatment. These findings may also inform the ongoing assessment of the FDA's safety advisories and any unintended public health consequences they may have. Specifically, the risks of suicidality associated with antidepressant medications need to be balanced against the risks of untreated depression.

**Table 1:
Drugs included in Analysis**

Anafranil (clomipramine)	Pamelor (nortriptyline)
Asendin (amoxapine)	Parnate (tranylcypromine sulfate)
Aventyl (nortriptyline)	Paxil (paroxetine HCl)
Celexa (citalopram hydrobromide)	Pexeva (paroxetine mesylate)
Cymbalta (duloxetine)	Prozac (fluoxetine HCl)
Desyrel (trazodone HCl)	Remeron (mirtazapine)
Elavil (amitriptyline)	Sarafem (fluoxetine HCl)
Effexor (venlafaxine HCl)	Seroquel (quetiapine)
Emsam (selegiline)	Sinequan (doxepin)
Etrafon (perphenazine/amitriptyline)	Surmontil (trimipramine)
fluvoxamine maleate	Symbyax (olanzapine/fluoxetine)
Lexapro (escitalopram oxalate)	Tofranil (imipramine)
Limbitrol (chlordiazepoxide/amitriptyline)	Tofranil-PM (imipramine pamoate)
Ludiomil (maprotiline)	Triavil (perphenazine/amitriptyline)
Marplan (isocarboxazid)	Vivactil (protriptyline)
Nardil (phenelzine sulfate)	Wellbutrin (bupropion HCl)
nefazodone HCl	Zoloft (sertraline HCl)
Norpramin (desipramine HCl)	Zyban (bupropion HCl)

Table 2

Antidepressant use for individuals ages 5 - 21 in MEPS during calendar years 2002/2003 and 2005/2006.

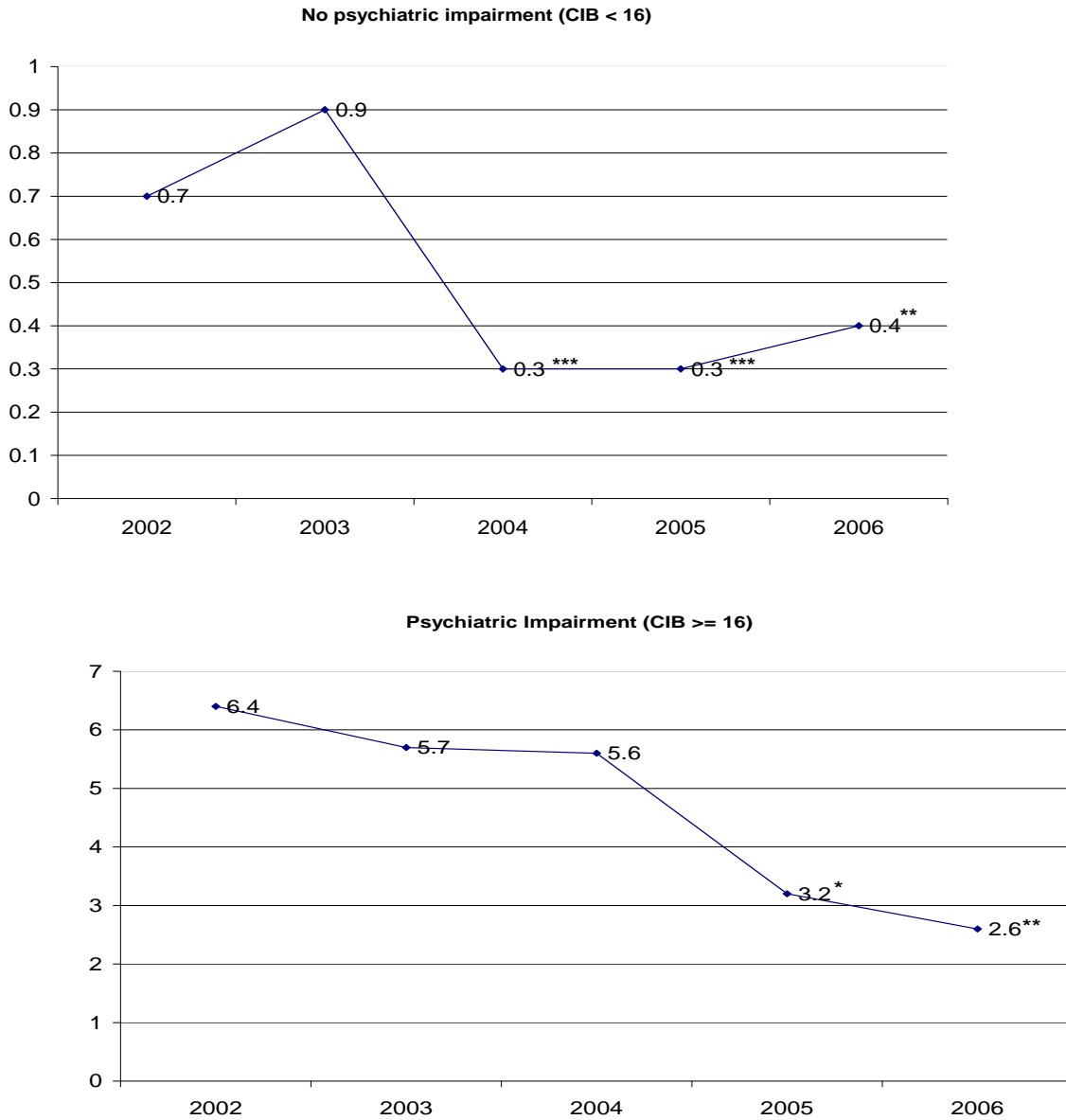
	2002-2003	2005-2006				95 %CI	
			Change	% Change	Odds Ratio	Lower	Upper
	N(unwtd), %(annual wtd) N(annual wtd)	N (unwtd), % (annual wtd) N (annual wtd)	% (annual wtd) N (annual wtd)				
Any Antidepressant (AD) use	475 2.91 2,004,724	335 2.16 1,492,542	- 0.76 - 512,182	-26.0	.734**	.605	.891
Experienced AD user	209 1.25 864,920	195 1.28 891,111	+0.03 +26,191	+ 2.4	1.024	.780	1.346
New AD user	266 1.65 1,139,804	140 0.87 601,431	- 0.78 - 538,373	- 47.2	.520***	.407	.665
Total population	68,943,981	69,358,504					

Note: All estimates reflect adjustment for complex weighting scheme of the MEPS.

*p<.10; **p<.05; ***p<.01

Figure 1

Adjusted probability of new antidepressant use by psychiatric impairment status among children ages 5 - 17 in MEPS during calendar years 2002-2006.

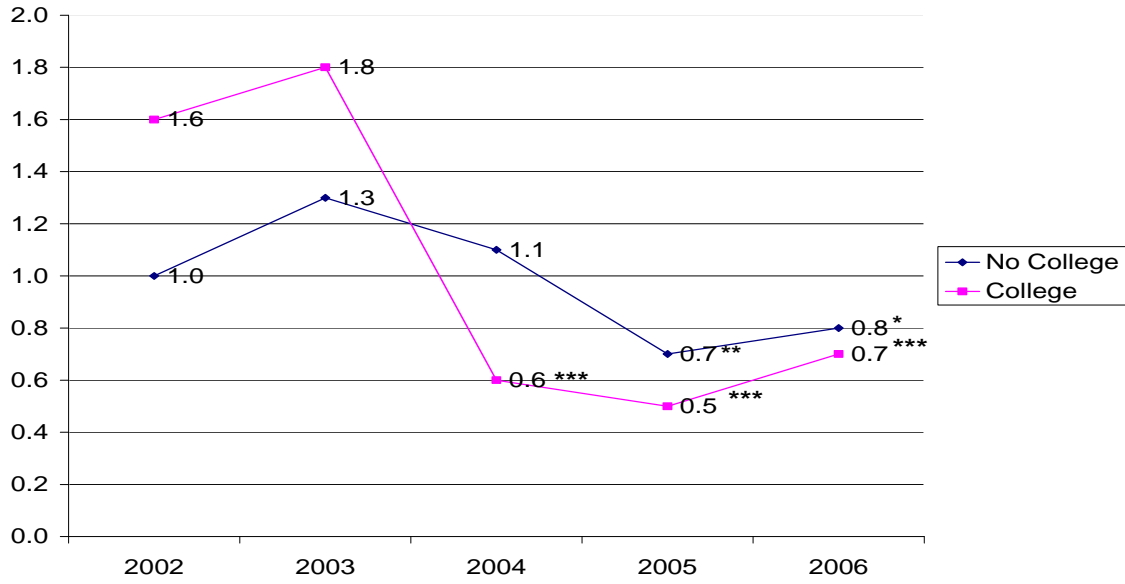


Note: Results adjusted by age, sex, whether low income, race/ethnicity, and insurance status; Significance levels indicate differences between noted year and 2003; *p<.10; **p<.05; ***p<.01.

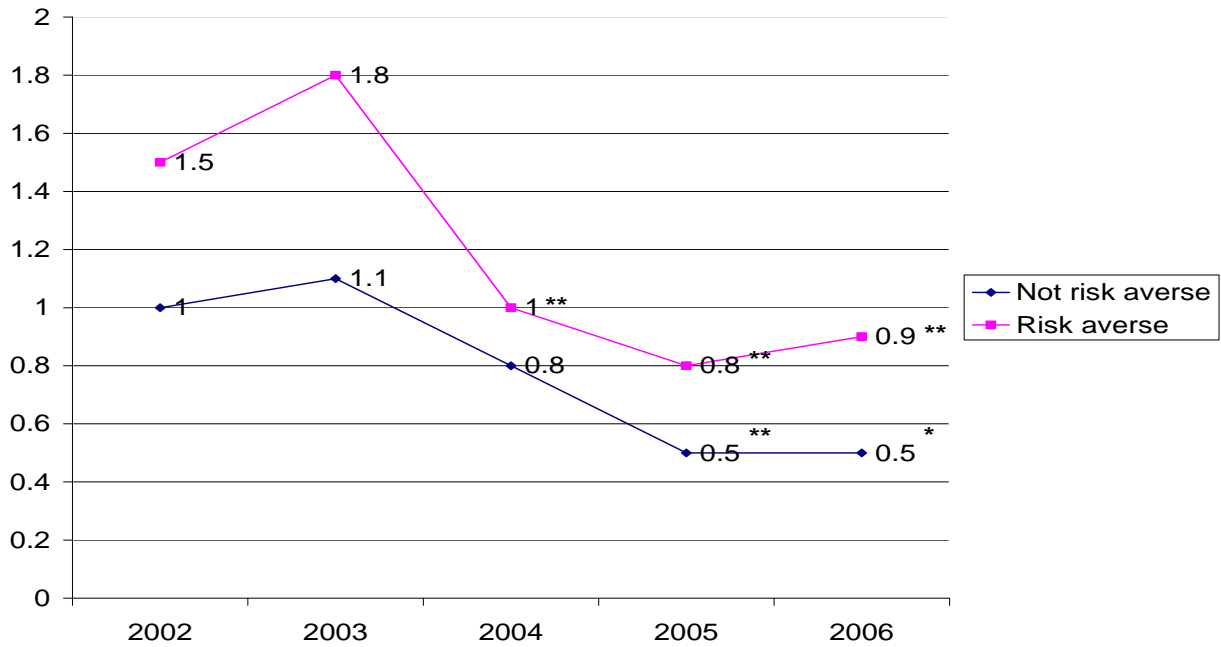
Figure 2

Adjusted probability of new antidepressant use by parent education and risk aversion among children ages 5 - 17 in MEPS during calendar years 2002-2006.

Panel A



Panel B



Note: Results adjusted by age, sex, whether low income, race/ethnicity, and insurance status;
Significance levels indicate differences between noted year and 2003; * $p < .10$; ** $p < .05$;
*** $p < .01$.

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