Decreased Use of Antidepressants in Youth After US Food and Drug Administration Black Box Warning

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ABSTRACT

Objective. This study evaluates changes in use of antidepressants in children and adolescents after the US Food and Drug Administration black box warning for increased risk of suicide.

Method. A retrospective chart review was completed for children and adolescents (ages 4–17) who were diagnosed with depressive or anxiety disorders in an outpatient clinic and offered a trial of antidepressants between September 2003 and February 2004 (before the black box warning) and between January 2005 and June 2005 (after the black box warning). Statistical analyses were performed with the SPSS version 17 and R package version 2.9.1. Univariate analysis was conducted using the Fisher's Exact test.

Results. The odds ratio calculated for the different groups suggests that in all the groups, the proportion of acceptance of antidepressant use was greater before the black box warning as compared to after the black box warning (odds ratio>1). It was also found that upon combining the age groups after the warning and comparing them, based on the diagnoses, there was a greater degree of refusal of antidepressant therapy when a diagnosis of anxiety disorder was made as compared to a diagnosis of depressive disorder (p=0.017).

Conclusion. There has been a decrease in the use of antidepressant therapy in children and adolescents following the US Food and Drug Administration black box warning for risk of suicide. A limitation of this study is that reasons for refusal of antidepressant therapy by parents or guardians of children and adolescents were not collected; therefore, there is no certainty that the black box warning was the primary reason for refusal.

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INTRODUCTION

In June 2003, the US Food and Drug Administration (FDA) issued an alert about a possible link between paroxetine treatment and suicidal behavior in youths.[1] Around the same time and for similar reasons, paroxetine was banned in the United Kingdom. In March 2004, the FDA made it a requirement of antidepressant drug manufacturers to include a warning on the official labeling of the drugs that there is a possible association between suicidal behavior and antidepressant use. In September 2004, the FDA's publicized advisory committee meeting culminated in a second public health advisory that was released in October 2004. This required a "black box" warning for all antidepressants about the risk of suicidality in pediatric patients.[2] The FDA's final action was based on data from randomized, controlled trials suggesting a twofold increase in suicidal ideation and behavior when antidepressants were prescribed to youths who were not actively suicidal.[3]

Shortly after the initiation of the black box warnings, Medco Health Solutions, at the request of the *New York Times*, conducted an analysis of its pharmacy benefit claims and found that the number of teenagers and children prescribed antidepressants had decreased by 18 percent.[4] Analyses of prescription-dispensing data conducted by NDC Health Atlanta from March 2004 to June 2005 revealed a 20-percent decrease in antidepressant prescriptions for children and adolescents.[5] A study by Libby et al[2] concluded that before the FDA advisory the rate of diagnosis of pediatric depression as well as rate of selective serotonin-reuptake inhibitor (SSRI) prescriptions for depression in youth was increasing, but after the advisory warning there was a substantial reversal. A similar decline in antidepressant prescriptions was reported by other studies,[6,7] with some reporting a shift in care from family doctors to psychiatrists for prescribing antidepressants in youths.[6]

The purported link between antidepressant medication use and suicide rates in youths has received substantial public attention. Some studies support a moderate increased risk of suicidality in pediatric patients treated with antidepressants,[8] though some find no increased risk during antidepressant treatment.[9] Conversely, a few studies demonstrate a decreased risk of suicide among youths treated with antidepressants.[10,11] In a recent study,[12] researchers looked at SSRI prescriptions and suicide rates for youths in the Netherlands from 2003 to 2005. They found that SSRI prescriptions for youths decreased while the youth suicide rate increased during that time. Authors of this study likened this finding to the documented increased youth suicide rates in the United States around the same time, which was the largest year-to-year change in suicide rates in this population since the Centers for Disease Control and Prevention began systematically collecting suicide data in 1979.[12] Between 1998 and 2003 in the United States, there was both a substantial increase in antidepressant prescription rates and a significant decrease in completed suicides in children and adolescents. Following the FDA warning, the trends for both antidepressant prescription rate and suicide among youths have reversed direction.[10–12] In contrast, one study performed in the United Kingdom[7] indicated no increase in suicidal behavior in youths despite the reduction in prescription of antidepressants to children and adolescents after the FDA warning. Some experts believe that it may be premature to draw conclusions based on year-to-year fluctuations in antidepressant prescriptions and youth suicides.[13]

A review of literature on the decrease in antidepressant prescription rates for youths after the FDA warning[2,3,11,12,14–16] suggests that physicians' reluctance to prescribe antidepressants to this age group could be one reason for this decline. Parents' or guardians' reluctance to accept this form of treatment for their children may also account for the decline in antidepressant use. We found just one study that looked into parental refusal rate after the FDA black box warning. Bhatia et al[14] developed and administered a survey to Nebraska clinicians to measure the impact of the FDA warning on prescribing practices. Participants represented general practitioners, pediatricians, psychiatrists (both child and adult), residents and fellows in training, nurse practitioners, and physician assistants. Although 77 percent had been prescribing antidepressants to children and teens before the warning, many reported writing fewer prescriptions for the medications after the warning was issued. Twenty-two percent of the participants had encountered caregivers or parents who refused antidepressant treatment for their children because of the black box warning. The study did not look into the rate of parental refusal prior to the black box warning. The present study examines the rates of refusal by guardians when physicians recommend antidepressants to children and youths seeking outpatient psychiatric treatment. Guardians' refusal rates prior to the FDA warning are compared to refusal rates following the warning.

METHOD

This study was conducted at the outpatient mental health clinic situated in a university setting in the Midwestern United States. The study was approved by the institutional review board of the institution. It was designed as a retrospective review of charts of "new patients" ages 4 to 17 years with a primary diagnosis of depressive or anxiety disorder who were offered trials of antidepressants and seen between September 2003 and February 2004 (before the black box warning) and January 2005 to June 2005 (after the black box warning). *New patient* was defined as a child or adolescent with no past

trials of any psychotropic medication and who was being seen by a psychiatrist or mental health professional for the first time. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM IV-TR*)[17] diagnostic criteria were used to identify a primary diagnosis of "depressive disorder," which included major depressive disorder, dysthymic disorder, or depressive disorder not otherwise specified (NOS). The primary diagnosis of anxiety disorder included generalized anxiety disorder, panic disorder with/without agoraphobia, social phobia, posttraumatic stress disorder, or anxiety disorder NOS. The age of the patients was also recorded. A second inclusion criterion for charts reviewed was documentation of refusal/acceptance of a trial of antidepressants by the guardians in all charts and discussion of FDA box warning in the charts from the post-FDA black box warning sample. Rejection of the trial of antidepressant was coded when the physician recommended a trial of an antidepressant and the guardian refused or said "no" to the antidepressant.

All patients were evaluated by a child and adolescent psychiatrist or a fellow in child and adolescent psychiatry supervised by a child and adolescent psychiatrist. Based on all inclusion criteria, charts of 134 children aged 4 to 12 years and 151 adolescents aged 13 to 17 years were reviewed to collect the data for the time period from September 2003 to February 2004. Charts of 132 children and 142 adolescents were reviewed to collect the data for the time period between January 2005 and June 2005. Among both before and after warning groups, 75 percent of children and 65 percent of adolescents were male. Review of charts revealed no documentation of any active suicidal thoughts expressed by any of the subjects during assessment. All the subjects included in the study were offered psychotherapy in addition to antidepressants.

Statistical analyses were performed with the SPSS version 17 and R package version 2.9.1. Univariate analysis was conducted using the Fisher's exact test.

RESULTS

The pre-FDA warning sample comprised 134 children and 151 adolescents who were offered a trial of antidepressants. Out of these, a review of charts revealed no documentation of any objection or refusal by the guardians in 121 children and 138 adolescents. Among children aged 4 to 12 years who were recommended antidepressants, 61 were diagnosed as having anxiety disorder and 73 were diagnosed with depressive disorder. Out of these, guardians of 56 children with anxiety disorders and 65 children with depressive disorders raised no objection to antidepressant. Among adolescents who were recommended antidepressant therapy, 71 were diagnosed as having anxiety disorder and 80 were diagnosed with depressive disorder. Out of these, guardians of 61 adolescents with anxiety disorder and 77 adolescents with depressive disorders raised no objection to antidepressant therapy.

Similarly, the post-FDA warning sample encompassed 132 children and 142 adolescents who were recommended antidepressants. Out of these, guardians of 95 children and 96 adolescents did not say "no" to the trial of antidepressant. Among children aged 4 to 12 years who were recommended antidepressants, 51 were diagnosed as having anxiety disorder and 81 were diagnosed with depressive disorder. Out of these, guardians of 34 children with anxiety disorders and 61 children with depressive disorders raised no objection to antidepressant therapy. Among adolescents who were recommended antidepressants, 52 were diagnosed as having anxiety disorder and 90 were diagnosed with depressive disorder. Out of these, guardians of 29 adolescents with anxiety disorder and 67 adolescents with depressive disorders raised no objection to antidepressant therapy.

The univariate analysis is presented in Table 1. In children with anxiety disorder, the percentage of children whose guardians agreed to treatment with an antidepressant significantly reduced from 91.8 percent (pre-warning, n=56) to 66.67 percent (post-warning, n=34) (p=0.0009) (i.e., a 25.13-percent increase in refusal). In children with depressive disorders, the percentage of children whose guardians agreed to antidepressant treatment significantly reduced from 89.04 percent (pre-warning, n=65) to 75.31 percent (post-warning, n=61) (p=0.0274) (i.e., a 13.72-percent increase in refusal).

In adolescents with anxiety disorders, the percentage of adolescents whose guardians agreed to antidepressants went down from 85.92 percent (pre-warning, n=61) to 55.77 percent (post-warning, n=29) (p=0.0002) (i.e., a 30.15-percent increase in refusal). In adolescents with depressive disorders, the percentage of adolescents whose guardians agreed to antidepressants went down from 96.25 percent (pre-warning, n=77) to 74.44 percent (post-warning, 67) (p=0.00008) (i.e., a 21.81-percent increase in refusal).

The odds ratio (OR) calculated for all the different groups suggests (as shown in Table 1) that in all the groups the proportion of acceptance was greater in pre-warning as compared to post-warning (OR>1).

It was also found that upon combining the age groups in the post-warning levels and comparing them based on the diagnoses, there was a greater degree of refusal to antidepressant therapy when a diagnosis of anxiety disorder was made as compared to a diagnosis of depressive disorder (p=0.017).

DISCUSSION

This is possibly the first study that specifically looks into any change in consumers' (guardians') acceptance of a trial of antidepressants in their children after the FDA black box warning. This is the first study to also compare the rate of rejection of a trial of antidepressants by guardians in pre- and post-FDA warning

TABLE 1. The guardian consent to take medication (before and after FDA warning)

AGE GROUP	DIAGNOSIS	WARNING	TOTAL	CONSENTED	REFUSED	INCREASE IN REFUSAL	CHI-SQUARE	*P*-VALUE	FISHER EXACT	ODDS RATIO
CHILDREN	Anxiety	Pre	61	56 (91.80%)	05 (08.20%)	25.13%	11.119	0.0009	0.001	5.51
		Post	51	34 (66.67%)	17 (33.33%)					
	Depressive	Pre	73	65 (89.04%)	08 (10.96%)	13.72%	4.867	0.027	0.036	2.65
		Post	81	61 (75.31%)	20 (24.69%)					
ADOLESCENTS	Anxiety	Pre	71	61 (85.92%)	10 (14.09%)	30.14%	13.896	0.0002	0.0001	4.77
		Post	52	29 (55.77%)	23 (44.23%)					
	Depressive	Pre	80	77 (96.25%)	03 (03.76%)	21.80%	15.545	0.00008	0.001	8.72
		Post	90	67 (74.44%)	23 (25.56%)					

periods. The study did not measure the actual reasons for refusal of a trial of antidepressants, and it is certainly possible that some cases of refusal might be unrelated to the FDA warning. The results demonstrate a substantial decrease in parents' or guardians' agreement with physicians' recommendations for antidepressants as treatment for anxious and/or depressed children and youths after the FDA black box warning. Refusal occurred despite a full evaluation by a mental health professional and recommendation of a trial of antidepressants for a primary diagnosis of anxiety or depression. Guardian refusal was significant in the depression group, but even more pronounced in the anxiety group. This finding could possibly be explained by less importance given to anxiety symptoms (considered less threatening) and less risks of complication, such as suicide, which is more often associated with depression.

The FDA's "risk of suicidality" labeling language for antidepressants is available on its website.[18] Although the FDA officially acknowledges no causal link, the agency nonetheless says at the beginning of the new "Warnings" section, "A causal role for antidepressants in inducing suicidality has been established in pediatric patients." Labeling surely does not explain this seemingly contradictory language. In fact, the language of the black box warning leaves little doubt that the agency believes there is a direct causal link between the 32 antidepressant medications currently marketed and increased suicidal thoughts and behaviors in youths. Parents want to protect their children. If they are told that an antidepressant might increase the risk of suicide, it is not surprising that they may reject the medication based on this information. It is imperative that parents and guardians be made aware that any risk from the use of antidepressants can be minimized by careful monitoring and that untreated depression carries a much higher risk of adverse outcome than risk of adverse outcome from antidepressant use, including suicide.[19–21] Most clinicians would agree that depression and anxiety can increase the likelihood of risky as well disruptive behavior and have a significant, long-term, negative effect on future relationships, productivity at work, and chances of having a successful, productive life. Parents should weigh these negative outcomes against the relatively small risk of suicidal behavior that may be associated with antidepressant use.

Study limitations. This study is a retrospective chart review, and all data were collected from a single outpatient clinic. Though the study included only charts (post-FDA warning) with documentation of discussion of the FDA warning, there is no certainty that the warning was the solitary reason for each parent's or guardian's refusal of a trial of antidepressants in his or her child. Furthermore, there were not sufficient data available to consider variation in refusal/acceptance of a trial of an antidepressant based on gender, severity of depressive/anxiety symptoms, or any past history of depression/anxiety.

CONCLUSION

In conclusion, these results suggest that, since the FDA black box warning, acceptance rates of

antidepressant trials in children and adolescents by their parents or guardians have significantly declined. This change appears to be most pronounced among guardians of anxious youths. This study provides no documentation of the decision-making process of the guardians, and the results could be due to the treatment decisions being based on risks/benefit analysis. The other possibility is that the FDA warning has frightened parents and guardians away from considering a trial of antidepressants for their children, even when recommended by the healthcare providers. If this is the case, there is a need to educate parents and guardians about the potential risks and benefits of antidepressant use in the treatment of anxiety and depressive disorders and the potential risks of untreated anxiety and depression in children and adolescents.

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