Psychiatr Q
DOI 10.1007/s11126-015-9389-8

ORIGINAL PAPER

Antidepressant Regulatory Warnings, Prescription Patterns, Suicidality and Other Aggressive Behaviors in Major Depressive Disorder and Anxiety Disorders

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Abstract In 2004 the Food and Drug Administration issued a warning on the risk of suicidality in children and adolescents receiving antidepressants. This was followed by reports of changes in antidepressant prescription patterns, suicidality and other aggressive behaviors, but debate is continuing regarding the nature and magnitude of these changes. We examined a large physician database for impact of the warning on antidepressant prescriptions, suicidality and other aggressive behaviors in major depressive disorder (MDD) and anxiety disorders in adult and pediatric patients. We analyzed electronic database covering over 100,000 patients, treated in Pre- (before 2003) and Post- (after 2004) warning periods. We compared strength of the association between the measures and the time period with two tests. Multivariate logistic regression analyses were performed to ascertain the unique effect of each parameter. Of 10,089 MDD (61.0 %) and anxiety disorders (39.0 %) patients, 65.2 % received antidepressant prescription and 16.1 % were pediatric patients. In post-warning period, there was a greater reduction in adult versus pediatric antidepressant prescription rates. Logistic modeling showed greater likelihood of antidepressant prescription in MDD as compared with anxiety disorders in post-warning period. Pediatric patients were more likely than adults to receive fluoxetine during the post-warning period. There was an overall reduction in suicidality and other aggressive behaviors in the post-warning period. Regulatory warnings may have had an impact on

Part of data Presented as Poster at Annual Meeting of American Psychiatric Association, San Francisco, CA, May 18–22, 2013.

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Published online: 25 August 2015

antidepressant benefit/risk assessment and consequent utilization, therapeutic effects, and adverse events. Our observations suggest that psychiatrists may heed regulatory warnings, but may also exert professional independence and discrimination in their application.

Keywords Antidepressant · Suicidality · Black box warning · Depression · Anxiety disorders · Prescription patterns · Aggressive behaviors

Introduction

Suicidal behavior is common in depression and suicide is the primary cause of increase mortality in this condition [1, 2]. Anxiety disorders are also associated with suicide, but to a lesser extent [3]. Antidepressants are a primary tool in the management of suicide and are recommended as first-line pharmacotherapy for major depressive disorder (MDD) and Anxiety disorders [4, 5]. However, while there are other first-line pharmacological treatments for anxiety disorders (e.g., benzodiazepines) antidepressants are the only standalone pharmacotherapy recommended for MDD [4].

Reports of suicidality and other aggression-related adverse events with antidepressant treatment date to the early days of antidepressant usage [6–8]. More recently, there were reports of increased deliberate self-harm events in patients prescribed selective serotonin reuptake inhibitors (SSRIs) [9], increase in suicidal acts in patients taking SSRIs than placebo [10], increase in suicidal behavior in first 9 days of an antidepressant treatment in patient aged 10–19 years [11], increased incidence of violence towards others in individuals using antidepressants [12] and heightened risk of deliberate self-harm in children and young adults initiating therapy with antidepressants [13]. Nevertheless, Bouvy and Liem reported negative association between increase in antidepressant prescriptions and suicidality and homicidality [14].

In 2003, the association between antidepressants and suicidality [9, 10] gained regulatory attention. In June 2003, the UK Medicines and Healthcare products Regulatory Authority (MHRA) issued an advisory against the use of paroxetine in young people, extending it to an advisory against the use of all SSRIs, except fluoxetine, in individuals under the age of 18 [15]. The United States Food and Drug Administration (FDA) followed with an advisory in March 2004 and 'Black Box' warning in October of 2004 on the risks of suicidality in children and adolescents receiving antidepressant treatment, emphasizing that fluoxetine is the only drug approved for use in pediatric depression [16]. In May 2007 black box warning was expanded to include young adults (18–24 years) [17]. The black box warning was based on a meta-analysis of 24 placebo-controlled studies where suicidality-related adverse events were twice as frequent with antidepressants when compared with placebo, roughly 4 versus 2 %, respectively. There were no completed suicides in this dataset [18].

The suicidality warnings were followed by reports of their impact on prescription patterns and disease management, suggesting an overall reduction in antidepressant prescriptions in the treatment of MDD [19–25], with a possible shift towards the use of fluoxetine in the younger age groups [19]. More recently, however, other studies failed to identify reduction in antidepressants prescription in MDD [26–28]. In addition, initially there were some reports of increase in suicidality, possibly associated with a decrease in antidepressant treatment [20] but these were challenged in further analyses [29]. The

conflicting and inconclusive reports of the impact of the regulatory warnings were the main motivation for our investigation. In addition, we had access to a unique and large physician prescription database, whereas the majority of studies in this area [13, 14, 19–25] had analyzed pharmacy claims data, with inherent limitations such as over-estimation of prescription counts [30], poor compliance measurement [31], and poor diagnostic accuracy [32].

Research Questions

This analysis examined four outcomes: (1) antidepressant prescription rate (2) fluoxetine prescription rate among prescribed antidepressants (3) suicidality rate (suicidal ideations, plans and acts) (4) other aggressive behaviors (homicidality rate; violent events; other aggression events). For each of these outcomes, the primary question was the relationship between pre- and post-warning period. Secondary questions were the differential effect on pediatric patients (<18 years old) versus adults and the impact on the management of MDD versus anxiety disorders.

Method

Source of Data

The source of the data is the Clinical Research Information System (CRIS), a consortium of treatment data from various psychiatric settings in the US. Beginning in 1998, CRIS has been administered through the Department of Psychiatry at Duke University Medical Center (DUMC). DUMC is a tertiary-care center with inpatient facilities, emergency room and outpatient clinics. Using MindLinc, a detailed psychiatric-care electronic database, we have compared treatment patterns and outcomes in over 100,000 patients treated at DUMC. Our dataset includes: (1) large patient visit level data with comprehensive details of each visit, (2) long duration of records before and after FDA warning (from January 1, 2000, through September 17, 2009) and, (3) specialist (psychiatrist) management.

Measures in the Analysis

Age consisted of two groups: pediatric patients (under 18 years old) and adults (18 years and older). Demographic characteristics included gender and race. Race was defined as white, black, 'other race', and 'missing'. Initial severity was expressed by Clinical Global Impression-Severity scores (CGI-Severity scores) at first encounter. Scores ranged from 1 (normal or near normal) to 7 (severe). Medication use examined whether or not the patient received an antidepressant and, if so, whether or not fluoxetine was prescribed. Suicidality, homicidality, violent events and other aggression events were analyzed using logistic regression models. Patients were selected who had received treatment, defined as two or more clinical encounters, in either the pre-black box period, from January 1, 2000 and prior to October 1, 2003, or the post-black box period, beginning on October 1, 2004 and ending September 17, 2009. Patients who had treatment spanning the two periods were excluded from this analysis. Patients who had only one encounter in the database were excluded.

Data Analyses

The analysis of each outcome measure proceeded in three steps: first the characteristics of the sample were determined, in total and by pre- versus post-black box. The strength of the association between the measures and the time periods were assessed with χ^2 measures of association. Secondly, bivariate relationships between the parameters and the outcome measures were determined, the strength of the relationship again being assessed by χ^2 tests. Finally, multivariable logistic analyses were performed to ascertain the unique effect of each parameter, controlling for effects of other measures. All analyses were conducted by SAS 9.3 [33].

The independent variable, whether pre- or post-black box, was defined with 'pre' consisting of events prior to October 1, 2003, and 'post' consisting of events occurring on or after October 1, 2004. Two-way interaction terms, between age and pre- versus post-black box and between diagnosis and pre- versus post-black box, were created to examine

Table 1 Characteristics of All MDD/anxiety disorders patients (N = 10,089)

Parameter	Total n (%)	Pre-black box n (%)	Post-black box n (%)	χ^2 (df) p value
Gender				
Male	3676 (36.5)	916 (35.2)	2760 (36.8)	2.4 (1) 0.121
Female	6413 (63.5)	1688 (64.8)	4725 (63.0)	
Race				
White	6988 (69.3)	1794 (68.9)	5194 (69.4)	79.1 (3) < 0.0001
Black	1984 (19.7)	449 (17.2)	1535 (20.5)	
Others	370 (3.7)	74 (2.8)	296 (3.6)	
Missing	747 (7.4)	287 (11.0)	460 (6.1)	
Age group				
Pediatric patient	1625 (16.1)	139 (5.4)	1486 (19.6)	301.2 (1) < 0.0001
Adults	8464 (83.9)	2465 (94.7)	5999 (80.1)	
Diagnosis				
MDD	6170 (61.0)	1862 (71.5)	4308 (57.6)	158.3 (1) < 0.0001
Anxiety disorders	3919 (39.0)	742 (28.5)	3177 (42.5)	
CGI severity score				
1	207 (2.1)	117 (4.5)	118 (1.2)	582.5 (6) < 0.0001
2	393 (3.9)	211 (8.1)	244 (2.4)	
3	1557 (15.4)	593 (22.8)	1273 (12.5)	
4	3905 (38.7)	1030 (39.6)	4346 (42.6)	
5	2829 (28.0)	480 (18.4)	3033 (29.7)	
6	1102 (11.0)	164 (6.3)	1088 (10.7)	
7	96 (1.00)	9 (0.3)	93 (0.9)	
Antidepressant prescribed				
Overall	6577 (65.2)	2054 (78.9)	4523 (60.4)	289.8 (1) < 0.0001
Fluoxetine[#]	1257 (19.1)	345 (16.8)	912 (20.2)	10.41 (1) 0.0013

MDD major depressive disorder, *CGI* clinical global impression, *DUMC* Duke University Medical Center

[#] Amongst the patients who were prescribed antidepressant (N = 6577), if patients were prescribed fluoxetine

Table 2 Bivariate analysis for antidepressants prescription and if antidepressant prescribed being fluoxetine

	Antidepressant not prescribed N = 3512 (34.8 %)	Antidepressant prescribed N = 6577 (65.2 %)	Wald χ^2 (df) p-value	Fluoxetine not prescribed# N = 5320 (80.9 %)	Fluoxetine prescribed# N = 1257 (19.1 %)	Wald χ^2 (df) p-value
Main effects						
Antidepressant prescription						
Pre-black box	550 (21.1)	2054 (78.9)	121.1 (1) <0.0001	1709 (83.2)	3457 (16.8)	1.74 (1) 0.187 (NS)
Post-black box	2962 (39.6)	4523 (60.4)		3621 (79.8)	912 (20.2)	
Gender						
Male	1388 (37.8)	2288 (62.2)	4.25 (1) 0.04	1857 (81.2)	431 (18.8)	5.17 (1) 0.003
Female	2124 (33.1)	4389 (66.9)		3463 (80.7)	826 (19.3)	
Race						
White	2259 (32.3)	4729 (67.7)	76.8 (3) <0.0001	3790 (80.1)	939 (19.9)	12.8 (3) 0.005
Black	785 (39.6)	1199 (60.4)		1005 (83.8)	194 (16.2)	
Others	146 (39.5)	224 (60.5)		181 (80.8)	43 (19.2)	
Missing	322 (43.1)	653 (56.9)		344 (80.9)	81 (19.1)	
Age group						
Pediatric patient	931 (57.3)	694 (42.7)	31.9 (1) <0.0001	410 (59.1)	284 (40.9)	0.43 (1) 0.513 (NS)
Adults	2581 (30.5)	5883 (69.5)		4910 (83.5)	973 (16.5)	
Diagnosis						
MDD	1687 (27.3)	4483 (72.7)	12.5 (1) 0.0004	3634 (81.1)	849 (18.9)	11.7 (1) 0.0006
Anxiety disorders	1825 (46.6)	2094 (53.4)		1686 (80.5)	408 (19.5)	

Table 2 continued

	Antidepressant not prescribed N = 3512 (34.8 %)	Antidepressant prescribed N = 6577 (65.2 %)	Wald χ^2 (df) p-value	Fluoxetine not prescribed[#] N = 5320 (80.9 %)	Fluoxetine prescribed[#] N = 1257 (19.1 %)	Wald χ^2 (df) p-value
CGI Severity Score						
1	91 (44.0)	116 (56.0)	159.2 (1) <0.0001	93 (80.2)	23 (19.8)	0.30 (1) 0.582 (NS)
2	140 (35.6)	253 (64.4)		203 (80.2)	50 (19.8)	
3	685 (44.0)	872 (56.0)		743 (85.2)	129 (14.8)	
4	1336 (34.2)	2569 (65.8)		2102 (81.8)	467 (18.2)	
5	881 (31.1)	1948 (68.9)		1524 (78.2)	424 (21.8)	
6	331 (30.0)	771 (70.0)		617 (80.0)	154 (20.0)	
7	48 (50.0)	48 (50.0)		38 (79.2)	10 (20.8)	
Interaction effects						
Pediatric patient * pre-black box	63 (45.3)	76 (54.7)	1.9 (1) 0.17	67 (88.2)	9 (11.8)	21.65 (1) <0.0001
Pediatric patient * post-black box	868 (58.4)	618 (41.6)		343 (55.5)	275 (44.5)	
Adults * pre-black box	487 (19.8)	1978 (80.2)	Same as above	1642 (83.0)	336 (17.0)	Same as above
Adults * post-black box	2094 (34.9)	3905 (65.1)		3268 (83.7)	637 (16.3)	
Anxiety disorders * pre-black box	205 (27.6)	537 (73.4)	Same as below	474 (88.3)	63 (11.7)	Same as below
Anxiety disorders *post-black box	1620 (51.0)	1557 (49.0)		1212 (77.8)	345 (22.2)	
MDD * pre-black box	345 (18.5)	1517 (81.5)	4.9 (1) 0.03	1235 (81.4)	282 (18.6)	3.56 (1) 0.06 (NS)
MDD * post-black box	1342 (31.1)	2966 (68.9)		2399 (80.9)	567 (19.1)	

MDD major depressive disorder, *CGI* clinical global impression, *NS* not significant

[#] Amongst patients prescribed antidepressants

the question of whether the relationship between age and prescription, between diagnosis and prescription, between age and suicidality and other aggressive behaviors and between diagnosis and suicidality and other aggressive behaviors were constant across time periods.

Results

Characteristics of the Population

Table 1 presents the characteristics of the population. 10,089 patients met inclusion criteria. There were 6170 patients with MDD (61.0 %) and 3919 (39.0 %) with anxiety disorders diagnoses. There were 2604 patients in the pre-black box period and 7485 patients in the post-black box period. Women outnumbered men (63.5 vs. 36.5 %); 69.3 % were white, 19.7 % African-American, and 3.7 % of other races. Pediatric patients, under the age of 18, constituted 16.1 % of the population, adults constituted the rest. 38.7 % patients were characterized as being moderately ill at the time of their initial diagnosis (CGI-Severity 4), 40.0 % were diagnosed as more severely ill (CGI-Severity score more than 4), and 21.3 % were characterized as being mildly ill (CGI-Severity score less than 4). In all, 65.2 % of the patients received a prescription for an antidepressant, of which 19.1 % received fluoxetine.

Antidepressant Prescriptions

Table 2 presents bivariate associations between selected parameters and whether or not an antidepressant was prescribed. Women, whites, adults and MDD patients were significantly more likely to be prescribed an antidepressant than were men, blacks, pediatric and anxiety disorders patients, respectively (for gender $p = 0.04$; for race and age group $p < 0.0001$; for diagnosis $p = 0.0004$). There was significantly more likelihood of an antidepressant prescription, if the illness was more serious at presentation (CGI >4; $p < 0.0001$).

Table 3 Logistic regression of antidepressant prescription/fluoxetine prescription amongst patients prescribed antidepressants

Parameter	Prediction of antidepressant prescription			Prediction of fluoxetine prescription[#]		
	AOR	Lower CI	Upper CI	AOR	Lower CI	Upper CI
Post-black box	0.34	0.28	0.41	1.23	0.90	1.68
Female	1.10	1.0	1.20	1.17	1.02	1.34
White	1.50	1.35	1.68	1.37	1.15	1.63
Pediatric patient	0.35	0.24	0.51	0.79	0.39	1.61
MDD	1.5	1.18	1.79	1.68	1.25	2.26
Initial CGI severity	1.30	1.25	1.36	1.02	0.96	1.08
Pediatric patient * post-black box	1.31	0.89	1.92	5.81	2.77	12.19
MDD * post-black box	1.30	1.03	1.63	0.72	0.51	1.01

MDD major depressive disorder, *CGI* clinical global impression, *AOR* adjusted odds ratio, *CI* class interval

[#] Amongst patients prescribed antidepressants

Table 4 Logistic regression of suicidality, homicidality, violent events and other aggressive events

Parameter	Suicidality			Homicidality			Violent Events			Other Aggressive Events		
	AOR	Upper CI	Lower CI	AOR	Upper CI	Lower CI	AOR	Upper CI	Lower CI	AOR	Upper CI	Lower CI
Post-black box	0.38	0.26	0.54	0.31	0.18	0.54	0.30	0.14	0.63	0.36	0.25	0.50
Male	1.22	1.12	1.33	1.88	1.60	2.22	2.19	1.75	2.75	1.27	1.71	1.38
White	0.77	0.70	0.84	0.47	0.40	0.56	0.42	0.33	0.52	0.70	0.65	0.77
Pediatric patient	1.72	1.99	2.46	0.82	0.48	1.43	1.10	0.54	2.25	1.59	1.13	2.22
MDD	5.33	3.82	7.43	0.91	0.46	1.81	0.81	0.28	2.37	4.04	2.91	5.61
Initial CGI severity	5.20	4.75	5.68	4.18	3.46	5.03	4.14	3.20	5.36	5.28	4.84	5.76
Pediatric patient * post-black box	1.75	1.20	2.55	2.16	1.20	3.90	1.46	0.67	3.15	1.71	1.20	2.43
MDD * post-black box	1.72	1.41	2.09	2.51	1.57	4.02	1.37	0.72	2.62	1.88	1.55	2.28

MDD major depressive disorder, *CGI* clinical global impression, *AOR* adjusted odds ratio, *CI* class interval

Antidepressants were less likely to be prescribed, overall, in post-black box period (78.9 % 'pre', vs. 60.4 % 'post'; $p < 0.0001$), with both MDD (81.5 % 'pre' vs. 68.9 % 'post') and anxiety disorders patients (73.4 % 'pre' vs. 49.0 % 'post') experiencing significant antidepressant prescription decline in in post-black box period (both at $p = 0.03$).

Logistic Models of Antidepressant Prescription

Table 3 presents adjusted logistic model of prescribed antidepressants. With other covariates controlled, females (AOR 1.10; 95 % CI 1.0–1.2) were more likely than men, whites were more likely than blacks (AOR 1.50; 95 % CI 1.35–1.68), MDD patients (AOR 1.5; 95 % CI 1.18–1.79), overall, more likely than anxiety disorders patients to receive an antidepressant. Further, pediatric patients as compared to adults (AOR 0.35; 95 % CI 0.24–0.51) were significantly less likely, overall, to be prescribed an antidepressant. In addition, the more serious the illness, the greater was the likelihood of an antidepressant being prescribed (CGI >4; AOR 1.30; 95 % CI 1.25–1.36). Finally, MDD patients, when compared with anxiety disorders patients (AOR 1.30; 95 % CI 1.03–1.63), were significantly more likely to receive an antidepressant in post-black box period. In other words, the higher percentage of antidepressant prescriptions in MDD versus anxiety disorders already existing in pre-black box period (81.5 % MDD versus 73.4 % anxiety disorders) significantly increased in the post-black box warning period (68.9 % MDD versus 49.0 % anxiety disorders; $p = 0.03$), even though both disorders experienced a decline in antidepressant prescriptions.

The Prescription of Fluoxetine Among Antidepressants

Table 2 presents the bivariate associations between the various measures and the selection of fluoxetine among the antidepressants prescribed to those patients receiving an antidepressant. Females (19.3 vs. 18.8 %; $p = 0.003$), whites (19.9 vs. 16.2 %; $p = 0.005$), and anxiety disorders patients (19.5 vs. 18.9 %; $p = 0.0004$) were significantly more likely to be prescribed fluoxetine than men, blacks and MDD patients respectively. Pediatric patients were significantly more likely to receive fluoxetine in the post-black box period (11.8 % 'pre' to 44.5 % 'post'; $p < 0.0001$).

Logistic Models of Fluoxetine Prescription

Table 3 presents adjusted logistic model for fluoxetine prescription among patients receiving an antidepressant. With covariate effects controlled, females were more likely than males (AOR 1.17; 95 % CI 1.02–1.34), whites (AOR 1.37; 95 % CI 1.15–1.63) were more likely than blacks, MDD patients more likely than anxiety disorders patients (AOR 1.68; 95 % CI 1.25–2.26) to be prescribed fluoxetine. Pediatric patients were more likely than adults (AOR 5.8; 95 % CI 2.77–12.19) to receive fluoxetine prescription in the post-black box period.

Logistic Models of Suicidality and Other Aggressive Behaviors

Table 4 presents adjusted logistic models for suicidality and other aggressive behaviors. Suicidality decreased after the black box warning (AOR 0.38; 95 % CI 0.26–0.54). Overall, suicidality was more frequent in MDD than anxiety disorders patients (AOR 5.33;

95 % CI 3.82–7.43), in pediatric patients than adults (AOR 1.72; 95 % CI 1.20–2.46), in those who had higher CGI score (CGI >4; AOR 5.20; 95 % CI 4.75–5.68), and who were male (AOR 1.22; 95 % CI 1.12–1.33). Suicidality was found to be less frequent in white patients than black patients (AOR 0.77; 95 % CI 0.70–0.84). Suicidality continued to be more frequent in post-black box warning period in MDD patients when compared with anxiety disorder patients (AOR 1.72; 95 % CI 1.41–2.09) and in pediatric patients when compared with adult patients (AOR 1.75; 95 % CI 1.20–2.55).

Homicidality decreased after the black box warning (AOR 0.31; 95 % CI 0.18–0.54). Homicidality was found to be more frequent in patients who had higher CGI score (CGI >4; AOR 4.18; 95 % CI 3.46–5.03) or were male (AOR 1.88; 95 % CI 1.60–2.22). Homicidality was found to be less frequent in white patients than black patients (AOR 0.47; 95 % CI 0.40–0.56; $p < .0001$). Homicidality was more frequent in post-black box warning period in MDD patients than in anxiety disorder Patients (AOR 2.51; 95 % CI 1.57–4.02) and in pediatric patients when compared with adult patients (AOR 2.16; 95 % CI 1.20–3.90).

Violent events decreased after the black box warning (AOR 0.30; 95 % CI 0.14–0.63). Violent events were found to be more frequent in patients who had higher CGI score (CGI >4; AOR 4.14; 95 % CI 3.20–5.36) or were male (AOR 2.19; 95 % CI 1.75–2.75). Violent events were found to be less frequent in white patients than black patients (AOR 0.42; 95 % CI 0.33–0.52).

Other aggression events decreased in the post-black box warning period (AOR 0.36; 95 % CI 0.25–0.50). Other aggression events were found to be more frequent in MDD patients than anxiety disorders patients (AOR 4.04; 95 % CI 2.91–5.61; $p < .0001$), in pediatric patients than in adults (AOR 1.59; 95 % CI 1.13–2.22), in patients who had higher CGI score (CGI >4; AOR 5.28; 95 % CI 4.84–8.76), or male patients (AOR 1.27; 95 % CI 1.17–1.38; $p < .0001$). Other aggression events were less in white patients than black patients (AOR 0.70; 95 % CI 0.65–0.77; $p < .0001$). Other aggression events continued to be more frequent in post-black box warning period in MDD patients (AOR 1.88; 95 % CI 1.55–2.28) and in pediatric patients (AOR 1.71; 95 % CI 1.20–2.43).

Discussion

This study examined antidepressant prescription patterns, suicidality and other aggressive behaviors before and after FDA black-box warning using data collected at psychiatrist visit level at Duke University Medical Center (DUMC). The majority of previous studies [13, 14, 19–25] had analyzed data derived from pharmacy claims, which have limitations such as over-estimation of prescription counts [30], poor compliance measurement [31], and poorer diagnostic accuracy [32] in comparison to psychiatrist visit level data and thus may provide limited information on this complex disease management decision-making process. Data from psychiatrist visits likely provide more accurate diagnostic information and better treatment decision-making. Management by psychiatrists may indicate presence of more severe cases [34] though. In addition, our analyses included only patients who had at least two consecutive visits to psychiatrist. The second visit allowed the psychiatrists to re-assess the diagnosis, treatment response and compliance aspects relevant to pre/post-black box comparisons. Although the warnings were intended for children and young adults, we studied adult age groups as well following suggestions from literature. We analyzed data

for MDD and anxiety disorders, the conditions subject to the greatest impact of the regulatory warnings.

Antidepressant Prescriptions in Post-black Box Warning

Pediatric Versus Adults Patients

Overall, our results suggest that antidepressants were less likely to be prescribed after the black box warning (AOR 0.34). Overall, the frequency of antidepressants prescriptions in pediatric patients was lower (AOR 0.35) in comparison with adult patients, but there was no significant difference in antidepressant prescriptions after black box warning in pediatric versus adult patients.

MDD Versus Anxiety Disorders Patients

MDD patients (AOR 1.30) were more likely than anxiety disorders patients to receive an antidepressant in post-black box warning period. These findings may reflect the fact that other effective treatments were available for anxiety disorders and that overall anxiety disorders are associated with less morbidity and mortality—hence presenting different benefit/risk consideration with regards to the antidepressant risk of suicidality. There was reduction in the relative proportion of MDD patients in post-black box period (71.5 % 'pre' to 57.6 % 'post') and a corresponding increase in anxiety disorders patients (28.5 % 'pre' to 42.5 % 'post') (Table 1). This may reflect reduction in the likelihood of making MDD diagnoses, as reported by others [35] or reduction in MDD patients seeking treatment when compared with anxiety disorders.

Overall Antidepressants Versus Fluoxetine Prescriptions

There was no significant overall difference in fluoxetine prescriptions between pre- and post-black box warning periods, but there were differences in fluoxetine prescriptions post-black box warning by age groups. Pediatric patients were significantly more likely than adults (AOR 5.81) to receive fluoxetine prescriptions in the post-black box period. The observed increase in fluoxetine prescriptions in pediatric patients might reflect substitution practices in post-black box warning period. This apparent preference for fluoxetine prescription over other antidepressants in pediatric patients is consistent with initial positive statements by the FDA in 2003 and 2004 about effectiveness of fluoxetine in treatment of pediatric depression [16].

Suicidality and Other Aggressive Behaviors in Post-black Box Warning

Suicidality (AOR 0.38) and other aggressive behaviors including homicidality (AOR 0.31), violent events (AOR 0.30) and other aggression events (AOR 0.36) decreased in post-black box warning period. Suicidality remained more frequent (AOR 1.75) in pediatric patients after the black box warning in comparison to adult patients. It is possible that more severe pediatric patients were included in post-black box period and that less severe pediatric depression patients received diagnoses other than MDD [35] or anxiety disorders, therefore being excluded from our analysis, leaving only the more severe patients in the dataset.

These results are consistent with causal effect between antidepressant usage and suicidality as proposed by the FDA. Several reports have speculated on the mechanism of antidepressants and suicidality and other aggressive behaviors hypothesizing that time course of overall improvement in depression may be distinct from the improvement in suicidal ideation and the possibility that some antidepressants have an effect on suicidality distinct from their effect on other aspects of depressive illness [8, 36]. Culpepper et al. proposed that somatic activation may precede cognitive improvement in suicidal patients [37]. They hypothesized this "activation syndrome" may cover variety of phenomena such as paradoxical worsening of depression, akathisia, insomnia, anxiety and panic attacks. They also made mention of undiagnosed bipolarity, non-response to treatment, drug–drug interaction as possible reasons for this phenomenon. They further proposed that at least in a subset of patients, the introduction of a SSRI or an increase in dose may result in an exaggerated initial decrease in serotonin transmission and, thus, enhance suicidality/aggressive behavior early in treatment.

Limitations

The retrospective and uncontrolled nature of our analyses limit conclusions regarding causality between the black-box warning, reduction in prescriptions of antidepressants, and changes in frequencies of suicidality and other aggressive behaviors. However, the large number of individuals and observations included in our database provide countering strengths. Data were collected at an academic institution, which may not reflect other settings. Further, we did not study the impact of black-box warning on attitude of patients including parents (in case of pediatric population) towards antidepressants, potentially an important variable influencing prescription patterns. Given that the media is a vital source of health related information [38] and findings about media coverage of antidepressant black-box warning are inconclusive [38], it is unclear what differential impact, if at all, the media may have had on providers, parents, adult and pediatric patients.

Conclusions

Our data suggest that antidepressants prescriptions decreased in post-black box warning period. Although this reductions was noted in both adults and pediatric patients, there was a greater reduction in adult. anxiety disorders patients experienced greater reduction in antidepressant prescriptions than MDD patients. Prescriber's decisions may reflect greater concern for suicidality in patients and in case of MDD with no treatment alternative other than antidepressants. Prescriptions of fluoxetine increased for pediatric patients in post-black box warning period. Overall suicidality and other aggressive behaviors were less in post-black box warning period. Suicidality continued to remain higher in post-black box period in pediatric patients compared to adult patients. Our observations suggest that psychiatrists may heed regulatory warnings, but may also exert professional independence and discrimination in their application.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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