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Health Advisories and Patterns of Patient Monitoring Among New Users of Antidepressant Medications

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Abstract

Introduction—In 2003, more intense monitoring of patients initiating antidepressants was advised because of emerging concerns of suicidality. We sought to identify patterns of patient monitoring after antidepressant initiation in British Columbia before and after issuance of health advisories.

Materials and Methods—We conducted a cohort study of antidepressant initiators between 1999 and 2005 using healthcare utilization data of all British Columbia residents. For the periods before (1999–2001) and after (2004–2005), health advisories concerning suicidality associated with antidepressants, we assessed monitoring intensity by calculating weekly physician and psychotherapy visit rates since antidepressant initiation. We also estimated monitoring patterns as the proportion of individuals who received weekly in-person contact during the first 4 weeks of treatment, then biweekly visits for 4 weeks, and then a visit at 12 weeks, as a proxy for intensive monitoring.

Results—Patterns of monitoring intensity were similar before and after the health advisories, but the level of intensity was lower after the advisory period. Overall, monitoring intensity peaked in the 4 weeks after antidepressant initiation. Weekly numbers of visits per subject during these 4 weeks were between 0.44 and 0.49 before the advisory and from 0.39 to 0.44 after the advisory. Among all initiators stratified by year of initiation, between 21% and 25% received intensive monitoring, and this proportion generally decreased on a yearly basis.

Discussion—Monitoring intensity for patients with depression initiating antidepressants decreased after the period of emergence and greater awareness of the association between antidepressants and suicidality.

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Dr Gagne takes full responsibility for the integrity of the data and the accuracy of the data analysis. All authors had full access to all the data in the study.

AUTHOR DISCLOSURE INFORMATION

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Keywords

antidepressants; monitoring; health advisories

Several studies have identified an association between antidepressant medications and suicidal behavior, particularly among children and adolescents receiving selective serotonin reuptake inhibitors.¹⁻³ Beginning in 2003, the findings of these studies prompted regulatory agencies worldwide, including the Committee on Safety of Medicines in the United Kingdom, the US Food and Drug Administration (FDA), and Health Canada, to alert providers to this emerging drug safety issue.⁴⁻⁸ The US FDA recommended that patients initiating antidepressant medications be observed closely for indications of suicidality.⁹ Similarly, Health Canada did not discourage the use of antidepressant medications but urged more intense monitoring of both young and adult users of these drugs, particularly shortly after treatment initiation.⁷

Two recent studies in the United States found that few patients treated with antidepressants actually receive monitoring in accordance with the FDA recommendations^{10,11} and that the intensity of monitoring did not change after the FDA issued its advisory.¹¹ Although 1 study found no influence of warnings on new antidepressant prescription rates in Ontario,⁸ another study using data from Manitoba found that antidepressant prescribing decreased significantly after the issuance of health advisories.¹² Still, little is known about the impact the advisories had on patterns of patient monitoring in Canada. The objective of this study was to identify patterns of patient monitoring after initiation of antidepressant therapy in British Columbia (BC), Canada in the periods before and after the health advisories.

MATERIALS AND METHODS

Data Source

Prescription data were obtained from the PharmaNet database, which contains records of all prescriptions dispensed at community pharmacies in BC, regardless of payer. Prescription records were linked by encrypted personal health numbers to administrative databases for physician services and hospitalizations, which are maintained by the Ministry of Health for all persons in its publicly funded healthcare system. Up to 25 diagnoses for hospital discharges and 1 diagnosis for each medical service are recorded in these databases with good specificity and completeness.¹³ Data were further linked to vital status information from the BC Vital Statistics Agency, the provincial vital statistics bureau.

Study Population

We conducted a cohort study among individuals with depression who were new initiators of antidepressant therapy between January 1, 1999 and December 31, 2005. New initiators were defined as those individuals who filled a first recorded (index) prescription for any antidepressant medication during the study period but with no antidepressant prescription record in the previous 6 months and who also had a physician visit or hospitalization with an *International Classification of Diseases, Ninth Edition* code for depression (296.2x, 296.3x, 309.0x, 309.1x, 311.xx) within the 6 months before or 2 months after the index date. A validation study found that such an algorithm has generally high sensitivity (71%), specificity (85%), and positive predictive value (86%).¹⁴ Initiators of bupropion were excluded because the use of this medication may have been indicated for smoking cessation rather than depression. Subjects were followed up until they stopped (defined by a more than 7-day gap in days' supply) antidepressant therapy, attempted suicide, died, left the province, or until the end of 12 months.

Outcome Measures and Analysis

We characterized the pattern of monitoring by calculating monitoring intensity as mean weekly physician and psychotherapy visit rates per individual after antidepressant initiation stratified by age group (<18, 18–25, 26–64, and >64 years old), calendar year of initiation, and provider type. Visits to chiropractors and podiatrists were excluded because these services were delisted in BC beginning in 2002. We examined monitoring intensity separately after the initiation of the index antidepressant medication and after the first change in antidepressant therapy during the same treatment episode. Changes in antidepressant therapy were defined as switches to a new antidepressant medication or addition of a second antidepressant drug.

We calculated the proportion of individuals who received a suggested intensive monitoring standard defined by weekly in-person contact (defined as either physician visits or psychotherapy sessions) during the first 4 weeks of treatment, then biweekly visits for 4 weeks, and then a visit at 12 weeks, which is a similar measure of monitoring intensity as used in other studies.^{10,11} We operationalized this monitoring schedule to allow some flexibility in the algorithm by calculating the proportion of patients with at least 4 visits by the end of the fourth week after the index date, with at least 6 such visits by the end of the sixth week, and with at least 7 visits by the end of the seventh week. We stratified these data by age group and calendar year of antidepressant initiation. We conducted Pearson χ^2 tests for homogeneity across age categories in each year and across years in each age category.

This study was approved by the institutional review board of the Brigham and Women's Hospital and signed data use agreements were in place.

RESULTS

A total of 227,537 new initiators of antidepressant medications were identified during the study period and included in the study cohort (Table 1). The mean age of study cohort members was 43 years, and about 56% were female. Approximately 0.6% of subjects had a suicide attempt in the prior year, and about 5% had a psychiatric hospitalization in the prior year. The absolute numbers and rates of new antidepressants initiators per 1,000 BC residents for each of the study years are shown in Table 2. An annual decrease in number and rates of new initiators is observable between 2000 and 2005.

Data aggregated by period of either before or after the interval during which the advisories were issued showed that monitoring intensity peaked in the 4 weeks after antidepressant initiation (Fig. 1). The average weekly number of visits per subject during these 4 weeks ranged from 0.44 to 0.49 before the advisory and from 0.39 to 0.44 after the advisory. Generally, monitoring rates stabilized between 0.20 and 0.35 weekly visits per subject by week 11. At all weekly time points after the index date up to week 39, the monitoring intensity was lower in the period after the health advisories compared with the period before the advisories. Similar intensity rates were observed beyond week 39. A similar pattern was also observed for monitoring after the first change in antidepressant therapy but without convergence of the trend lines in the latter portion of the follow-up window (Fig. 2).

Among all cohort members, the proportion of subjects who received intensive monitoring ranged from about 25% to 21% during the years 1999 to 2005, with a clear downward trend that was only temporarily slowed in 2004 (Table 3). In general, smaller proportions of individuals younger than 18 years received such monitoring compared with older subjects, with only 17% to 21% of children receiving intensive monitoring depending on the year of initiation. The 65 and older age group had the highest proportion of subjects with intensive monitoring.

DISCUSSION

In 2 cohorts of individuals with recorded diagnoses of depression who initiated antidepressant medications in BC before and after the health advisories, we found that the monitoring intensity slightly decreased from 1999 to 2005. This trend was not reversed after greater awareness of a possible association between antidepressants and suicidality, including warnings by Health Canada alerting health care providers. Correspondingly, the proportion of patients monitored according to an intensive monitoring schedule decreased steadily, reaching a low of only 17% of children newly started on antidepressant drugs in 2005.

The assessment of proportions of patients who received intensive monitoring stratified by year of antidepressant initiation revealed a very modest response to the health advisories as evidenced by slight increases in proportions across age groups in 2004. This seems to suggest that despite the general deterioration of monitoring of those with depression who initiate antidepressants, health advisories may have had some minor impact on health service utilization. However, this effect was not sustained into 2005.

Using a similar algorithm to measure intensive monitoring, Morrato et al¹¹ found that a much smaller proportion of patients received such monitoring in the United States after the period of health advisories. Similar to our findings, these investigators observed a very small and transient increase in the proportion of patients overall who received intensive monitoring after the advisory period compared with the period before the advisories. Stettin et al¹⁰ also found a general lack of response with regard to monitoring intensity after the period of health advisories in the United States.

We also observed an overall decrease in new antidepressant prescriptions, which was more pronounced in the years after the health advisories. This finding is consistent with decreases in new antidepressant prescriptions observed in Ontario⁸ and Manitoba,⁹ and in the United Kingdom in response to media publicity¹⁵ over the same period. This study adds to the growing body of literature that suggests that regulatory warnings may not be achieving their intended objectives and may actually lead to unintended consequences.

This analysis has several limitations. Measures of monitoring intensity were based on frequency of contact with the medical care system recorded in administrative databases, which cannot account for the quality of care received by patients at each encounter. In general, the frequency of monitoring was lowest among those younger than 18 years and greatest among those aged 65 and older. However, because all visits to all physicians were included in the analysis, this finding may reflect the lesser degree of comorbidity in children and adolescents and the relatively greater degree of comorbidity in the elderly, rather than the extent of monitoring specifically for depression in these patients. For example, routine visits to general practitioners were included in our assessment of monitoring intensity although they may not be intended specifically for depression care. In agreement with other authors,^{10,11} we believe that while care for depression may not have been explicitly coded for each visit, such encounters nevertheless provide an opportunity for the physician to provide care for depression. This may have overestimated the true intensity of monitoring specifically for depression. Because of this and of the slight overall diminishing temporal trend in monitoring that we observed, our measures may have been somewhat insensitive. However, including only medical encounters associated with depression diagnosis codes would likely have underestimated the true monitoring intensity.

To the best of our knowledge, specific monitoring recommendations for patients with depression who initiate antidepressants do not currently exist in Canada. Thus, we used a measure of intensive monitoring based on a suggested monitoring schedule originating in the United States. Similar measures have been used in other published studies.^{10,11} Importantly,

we used this monitoring schedule as a proxy for intensive monitoring to examine changes in monitoring intensity in the absence of other validated measures of appropriate monitoring of patients initiating antidepressant medications. The use of this measure was not intended as a benchmark to measure the monitoring performance of health providers and should not be interpreted as such.

In conclusion, monitoring intensity after initiation of antidepressant therapy for individuals with depression decreased in BC after advisories issued by several worldwide regulatory agencies, including FDA and Health Canada, that urged increased monitoring of these patients.

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FIGURE 1.

Weekly follow-up visits per patient after initiation of antidepressant medication in the periods before (1999–2001) and after (2004–2005) health advisories.

FIGURE 2.

Weekly follow-up visits per patient after initiation of antidepressant therapy change in the periods before (1999–2001) and after (2004–2005) health advisories.

TABLE 1

Baseline Characteristics of Antidepressant Initiators in BC, 1999–2005 (N = 227,537)

Characteristic	
Age, mean $\pm$ SD, yrs	43.4 $\pm$ 18.8
Female, n (%)	126,414 (56.6)
Number of distinct drugs, mean $\pm$ SD	5.3 $\pm$ 4.1
Comorbidity score, mean $\pm$ SD	0.2 $\pm$ 0.8
Comorbid diagnoses, n (%)	
ADHD	3232 (1.4)
Anxiety	8077 (3.6)
Dementia	1529 (0.7)
Mania	3029 (1.3)
Psychotic disorder	4872 (2.1)
Other psychiatric disorders	27,630 (12.1)
Substance abuse	8626 (3.8)
Suicide attempt in past year, n (%)	1446 (0.6)
Psychiatric hospitalization in past year, n (%)	11,104 (4.9)
Index drug	
Amitriptyline	16,260 (7.2)
Citalopram	49,112 (21.6)
Clompiramine	381 (0.2)
Desipramine	365 (0.2)
Doxepin	1153 (0.5)
Fluoxetine	14,039 (6.2)
Fluvoxamine	5038 (2.2)
Imipramine	1348 (0.6)
Mirtazapine	3756 (1.7)
Moclobemide	478 (0.2)
Nefazodone	3287 (1.4)
Nortriptyline	1661 (0.7)
Paroxetine	57,024 (25.1)
Sertraline	24,767 (10.9)
Trazodone	14,204 (6.2)
Trimipramine	812 (0.4)
Venlafaxine	33,790 (14.9)
Other antidepressants	62 (0.0)

TABLE 2

Annual Number and Rates of New Antidepressant Initiators in BC, 1999–2005

Year	No. Antidepressant Initiators	No. Initiators per 1000 Individuals [*]
1999	37,376	9.32
2000	38,978	9.65
2001	36,996	9.07
2002	33,716	8.19
2003	32,286	7.77
2004	25,961	6.18
2005	22,224	5.22

^{*} Denominator is total BC population in each year per BC population forecast available at: www.bcstats.gov.bc.ca/data/pop/pop/project/betab1.asp.

TABLE 3

Proportion of Individuals with at Least 12 Weeks of Follow-Up Who Received Intensive Monitoring* by Age Group and Year of Antidepressant Initiation

Year	All Initiators		<18 Years Old		18-25 Years Old		26-64 Years Old		≥65 Years Old		Homogeneity $P^{\dagger}$
	n	%	n	%	n	%	n	%	n	%	
1999	20,365	25.38	1224	20.34	1946	24.46	14,249	25.24	2946	28.72	<0.0001
2000	22,588	24.96	1670	18.98	2502	25.70	15,280	24.81	3136	28.32	<0.0001
2001	22,157	23.33	1835	21.04	2515	24.65	14,854	23.75	2953	21.50	0.0021
2002	21,066	22.03	1804	18.51	2522	23.71	13,838	21.61	202	24.71	<0.0001
2003	21,400	21.13	2054	18.11	2685	22.91	13,727	21.49	2934	19.90	0.0002
2004	17,982	22.68	1289	18.08	2543	23.44	11,505	22.35	2645	25.67	<0.0001
2005	12,750	21.33	915	16.94	1919	21.94	7951	21.48	1965	22.19	0.0077
Homogeneity $P^{\dagger}$		<0.0001		0.0899		0.0756		<0.0001		<0.0001	

* Suggested monitoring defined as weekly in-person contact during the first 4 weeks of treatment, followed by biweekly visits for 4 weeks, and then a visit at 12 weeks, based on monitoring parameter used by Stettin et al¹⁰ and Morrato et al.¹¹

[†] Pearson χ^2 tests were conducted to test for homogeneity across proportions of age categories in each year and across years in each age category. The P value for each test is reported.