Shifts in Propylthiouracil and Methimazole Prescribing Practices: Antithyroid Drug Use in the United States from 1991 to 2008

Ana B. Emiliano, Laura Governale, Mary Parks, and David S. Cooper

Division of Endocrinology and Metabolism (A.B.E., D.S.C.), Johns Hopkins School of Medicine, Baltimore, Maryland 21287; and Department of Health and Human Services (L.G., M.P.), Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Silver Spring, Maryland 20993

Context: The thionamide antithyroid drugs methimazole and propylthiouracil are the mainstay of pharmacologic therapy for Graves' disease. However, little is known about the rate of use of these drugs and the prescribing practices of physicians treating hyperthyroidism.

Objective: The objective of the study was to examine the frequency of methimazole and propylthiouracil use from years 1991 to 2008.

Methods: The data were acquired by the U.S. Food and Drug Administration's Division of Epidemiology through two databases: IMS National Sales Perspectives and the Surveillance Data, Inc. Vector One: National database.

Results: There was a 9-fold increase in the annual number of methimazole prescriptions during the study period, from 158,000 to 1.36 million per year. There was a 19% increase in the annual number of propylthiouracil prescriptions, from 348,000 to 415,000 per year. Propylthiouracil, which held two thirds of the market from 1991 to 1995, was surpassed by methimazole in 1996. Patient demographic data indicated that although 72% of methimazole prescriptions were for females, males were more likely to be on methimazole (82%) than females (74%) ($P < 0.001$, two tailed χ^2 test). The only demographic group in which methimazole use decreased was women of childbearing age (5% decrease, $P < 0.001$, two tailed χ^2). The incidence of hyperthyroidism in 2008 was estimated based on the number of new prescriptions of thionamides by age group and data from the 2008 U.S. census: 0.44 per 1000 for ages 0–11 yr, 0.26 per 1000 for ages 12–17 yr, 0.59 per 1000 for ages 18–44 yr, 0.78 per 1000 for ages 45–64 yr, and 1.01 per 1000 for ages 65+ yr.

Conclusions: Methimazole has become the most frequently prescribed antithyroid drug. The remarkable increase in the total number of dispensed thionamide prescriptions over the last 18 yr may indicate a trend toward pharmacological treatment as primary treatment of Graves' disease in the United States. **(*J Clin Endocrinol Metab* 95: 2227–2233, 2010)**

Since their introduction in the mid 1940s, the thionamide antithyroid drugs propylthiouracil (PTU) and methimazole (MMI) have continued to be the mainstay of pharmacologic treatment of Graves' disease in the United States (1). Thionamides exert their antithyroid effects primarily by inhibiting thyroid hormone synthesis through interference with the oxidation and organic binding of iodide into thyroglobulin (2). In addition, PTU, but not MMI, inhibits the peripheral conversion of T_4 to T_3 by type 1 deiodinase (3, 4). There are also incompletely understood effects of both PTU and MMI on the immune system, which may partly account for

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Abbreviations: MMI, Methimazole; PTU, propylthiouracil; VONA, Vector One: National.

the remissions seen after a course of antithyroid drug therapy (5), and the blunting of the rise in anti-TSH receptor antibody levels after radioiodine therapy in MMI-pretreated patients (6).

MMI and PTU can be used as primary therapy for Graves' disease or as preparation for surgery or radioactive iodine treatment. Although radioactive iodine treatment is the preferred treatment modality of hyperthyroidism in the United States for most adults (7), primary therapy with PTU and MMI continue to be common alternatives, with many patients remaining on them for years (8). Data from the early 1990s suggested that PTU was favored over MMI by endocrinologists in the United States (9). However, given its superior side effect profile, greater efficacy in severely hyperthyroid patients (10), and more favorable adherence rate related to its once-daily dosing (11), MMI has been recommended as the first-line agent, with PTU use relegated to specific clinical circumstances: allergy to MMI, Graves' disease in pregnancy, and possibly life-threatening thyrotoxicosis (thyroid storm) (2). The recommendation against the use of PTU as the first-line agent in children or adults has recently been strengthened as a result of increasing numbers of reports of severe liver toxicity, in some cases leading to transplantation and in a few, death from fulminant hepatic failure (12–14). Despite the recommendations to use MMI as the primary thionamide, the prescribing habits of clinicians caring for patients with hyperthyroidism are not known.

In the present study, we report the prescribing practices for PTU and MMI from 1991 to 2008. Using two pharmacy databases, we were able to estimate the total annual number of dispensed prescriptions for PTU and MMI during that time period, as well as the total number of newly dispensed thionamide prescriptions.

Materials and Methods

The data reported in this paper were acquired by the Division of Epidemiology, Office of Surveillance and Epidemiology of the U.S. Food and Drug Administration (FDA). Two databases were used: The IMS Health, IMS National Sales Perspectives database and the Surveillance Data, Inc. Vector One: National database. The IMS Health, IMS National Sales Perspectives database was used to estimate the sales of PTU and MMI in the United States in 2008. This database compiles the sales of drugs from manufacturers to retail markets, which include chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Use from mail order pharmacies (6–7% of sales) was not included in this analysis.

We examined prescription use trends for MMI and PTU for the years 1991 through 2008 using Surveillance Data's Vector One: National (VONA). Surveillance Data's VONA measures retail dispensing of medications to consumers via formal prescriptions. Information is available on physician specialty, the patient's age and gender, and estimates of the numbers of patients who are either continuing therapy or who are initiating therapy. The Vector One database integrates prescription activity from a variety of sources, including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One receives more than 2.0 billion prescription claims per year, representing more than 160 million unique patients. Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the United States. The pharmacies in the database account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Using these data, estimates for national drug prescription claims and demographic factors at the national level are derived by Surveillance Data.

Data on patient demographics were available for the years 2002–2008. Data on the frequency of new-to-therapy prescriptions were available for years 2005–2008. Prescriptions were classified as new-to-therapy prescriptions from the date of dispensing if no prescriptions were dispensed to a patient for either MMI or PTU in the previous 6 months. We used the number of new PTU and MMI prescriptions dispensed as a surrogate in the calculation of the annual incidence of hyperthyroidism. The total number of new-to-therapy PTU and MMI prescriptions for each age group in the FDA data (0–11, 12–17, 18–44, 45–64, and 65+ yr) were divided by the respective population from the projected 2008 census data on population by age groups (www.census.gov/popest/national/asrh/NC_EST2008-sa.html). Because the census data were reported in 21 age groups, we converted the information into five age groups, similar to the FDA report age distribution (0–9, 10–19, 20–44, 45–64, and 65+ yr). We report the estimated incidence per 1000 persons.

Finally, the databases also provided information on dispensed prescriptions by prescriber specialty.

Results

Based on the IMS Health, IMS National Sales Perspectives data, it can be estimated that PTU and MMI are distributed primarily in outpatient settings. In 2008 approximately 78% of MMI and 83% of PTU were distributed through retail pharmacies.

MMI and PTU dispensed outpatient prescriptions

Over the 18-yr period from 1991 to 2008, the total number of prescriptions dispensed annually for MMI increased nearly 9-fold, from approximately 158,000 in 1991 to nearly 1.36 million prescriptions in 2008 (Fig. 1). The total number of prescriptions includes new prescriptions, renewed prescriptions, and prescription refills. Annual dispensed prescriptions for PTU, on the other hand, increased only 19%, going from approximately 348,000 prescriptions in 1991 to approximately 415,000 prescriptions in 2008. PTU held approximately one half to two thirds of the market from 1991 through 1995; in 1996 dispensed prescriptions for MMI surpassed those for PTU, and MMI remained the most prescribed drug through the end of the study period. By 2008 MMI had about 77% of the market share.

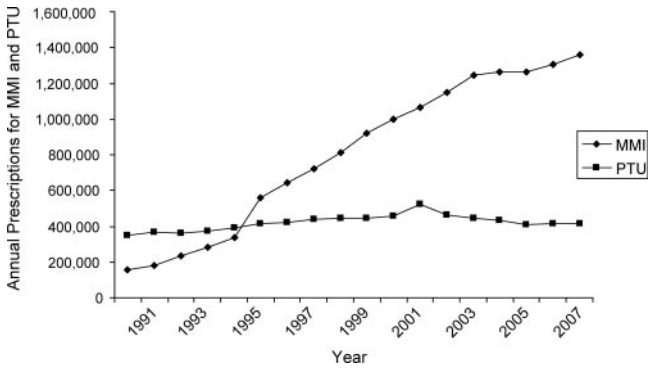

FIG. 1. Total number of prescriptions dispensed for MMI and PTU from outpatient retail pharmacies, 1991–2008, according to Surveillance Data, Vector One: National Database, extracted March 2009.

MMI and PTU prescription distribution by gender and age

Patient demographic data were available for 2002 through 2008. Table 1 depicts total numbers of prescriptions dispensed annually (new prescriptions and refills). The distribution of prescription use showed that nearly three quarters of MMI dispensed prescriptions were for females (Table 1). For example, in 2008, of approximately 1.36 million dispensed MMI prescriptions, 986,753 were for female patients (72%) and 348,544 for males (28%). Table 2 shows the numbers of individual unique patients receiving prescriptions in each calendar year. Whereas MMI use predominated in both sexes, MMI had a slightly lower proportion of use in the female population, compared with PTU from 2002 to 2008. For example, in 2008 proportionally fewer women (75%; 250,590 females on MMI/334,507 females, which is the total sum of females on both MMI and PTU) received MMI compared with males (82%; 91,912 males on MMI/111,563, which is the total sum of males on both MMI and PTU) ($P < 0.001$, two tailed χ^2 test) (Fig. 2). The data for PTU over this 7-yr period revealed that the number of dispensed prescriptions and patients receiving PTU decreased in all age groups, irrespective of gender (Tables 1 and 2), which is the opposite of what occurred in terms of MMI use. However, the use of MMI decreased in females in the 18- to 44-yr age group (Table 1). Unlike the other female age groups, in this subgroup there was a 5% decrease in dispensed prescriptions in year 2008 compared with the baseline, which is year 2002 ($P < 0.001$, two tailed χ^2) (Fig. 3).

TABLE 1. Total number of PTU and MMI prescriptions dispensed from retail pharmacies

	2002	2003	2004	2005	2006	2007	2008
PTU female total	418,380	373,223	354,192	346,491	329,896	330,256	332,857
Years							
0–11	3,350	2,947	2,822	2,725	1,798	1,736	1,917
12–17	8,254	7,093	6,138	5,500	4,556	4,873	4,364
18–44	163,295	141,147	129,991	123,143	114,387	112,900	112,709
45–64	128,579	116,759	112,381	112,209	108,370	108,456	108,714
65+	113,055	104,071	101,610	102,184	100,152	101,707	104,700
Unspecified	1,847	1,206	1,250	730	633	584	453
MMI female total	765,223	811,918	863,280	889,730	886,073	926,117	986,753
Years							
0–11	47,519	55,808	71,233	81,329	93,189	89,143	88,911
12–17	41,161	42,387	47,174	47,766	53,582	50,214	49,382
18–44	219,257	219,953	218,573	212,374	193,680	200,771	209,131
45–64	235,345	252,102	269,142	286,574	277,593	300,928	328,011
65+	192,070	200,464	217,058	239,123	247,740	268,365	296,554
Unspecified	29,871	41,204	40,100	22,564	20,289	16,696	14,764
PTU male total	101,863	91,129	86,716	84,640	80,006	81,480	80,498
Years							
0–11	1,544	1,276	1,075	955	826	675	634
12–17	2,908	2,372	1,854	1,913	1,706	1,691	1,330
18–44	31,947	27,224	25,015	23,006	21,771	21,692	20,050
45–64	38,156	35,373	34,402	34,003	32,570	33,097	32,802
65+	26,265	24,308	23,764	24,433	22,814	23,863	24,939
Unspecified	1,043	576	606	330	319	462	743
MMI male total	287,930	301,084	324,211	332,867	337,518	347,654	348,544
Years							
0–11	38,158	41,472	50,101	55,097	63,171	62,282	54,972
12–17	24,215	26,688	28,676	27,747	31,793	30,467	27,098
18–44	66,894	69,138	70,999	69,397	66,741	71,248	71,586
45–64	74,778	78,753	83,747	91,686	88,076	94,132	101,832
65+	54,424	53,144	59,331	66,027	65,318	70,206	76,831
Unspecified	29,461	31,889	31,357	22,913	22,419	19,319	16,225

Data source was Surveillance Data, VONA, extracted in 03/2009.

TABLE 2. Total number of patients receiving a prescription for PTU or MMI

	Projected patient count						
	2002	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
PTU female total	110,333	101,874	91,154	87,570	83,732	82,754	83,917
Years							
0–11	829	779	625	612	476	440	467
12–44	53,429	47,170	41,298	39,048	36,474	35,632	35,442
45–64	31,853	30,136	27,298	26,621	25,723	25,506	26,084
65+	23,201	22,130	20,244	19,781	19,623	19,689	20,532
Unspecified	1,021	1,659	1,689	1,508	1,436	1,487	1,392
MMI female total	209,321	235,978	235,419	230,568	230,257	234,823	250,590
Years							
0–11	14,410	15,702	18,951	20,703	24,324	22,943	23,543
12–44	83,631	81,927	77,955	75,954	72,098	72,449	74,639
45–64	64,099	67,649	67,711	70,250	67,901	72,227	79,562
65+	45,286	46,582	46,616	48,779	51,112	54,364	61,326
Unspecified	1,895	24,118	24,186	14,882	14,822	12,840	11,520
PTU male total	25,349	24,098	21,745	20,668	19,638	19,845	19,651
Years							
0–11	394	341	308	208	204	173	172
12–44	9,618	8,541	7,559	6,921	6,515	6,385	5,957
45–64	9,275	9,004	8,159	7,992	7,666	7,680	7,640
65+	5,923	5,788	5,290	5,203	4,924	5,201	5,389
Unspecified	139	424	429	344	329	406	493
MMI male total	74,428	87,011	89,075	87,505	90,493	91,159	91,912
Years							
0–11	11,753	11,604	13,575	14,041	16,759	16,187	15,094
12–44	27,452	27,570	27,118	26,109	26,637	27,133	27,538
45–64	20,123	21,187	20,849	22,119	21,297	22,325	24,169
65+	14,548	13,892	14,138	15,277	15,029	16,105	17,977
Unspecified	552	12,758	13,395	9,959	10,771	9,409	7,134

Data source was Surveillance Data, Total Patient Tracker, extracted March 2009.

New-to-therapy prescriptions

Newly dispensed MMI and PTU prescriptions were categorized as new to therapy by age group from years 2005 to 2008 (Table 3). Overall, in 2008 there were 190,327 new-to-therapy prescriptions dispensed for antithyroid drugs, which, assuming that most patients receive a prescription for an antithyroid drug at the onset of their disease, may represent a very rough estimate of the total number of new cases of hyperthyroidism in the United States in that year. There were 41,551 new-to-therapy prescriptions for PTU, or approximately 22% of the total. However, this fraction varied with age. For example, in young children aged 0–11 yr, the proportion receiving PTU was only 1.7% of the total, whereas in young and middle-aged women aged 18–44 yr, the proportion was 32%. Assuming that most hyperthyroid patients receive primary antithyroid drug therapy or receive antithyroid drugs for a few months before radioiodine therapy or surgery, we calculated an approximate annual incidence of hyperthyroid-

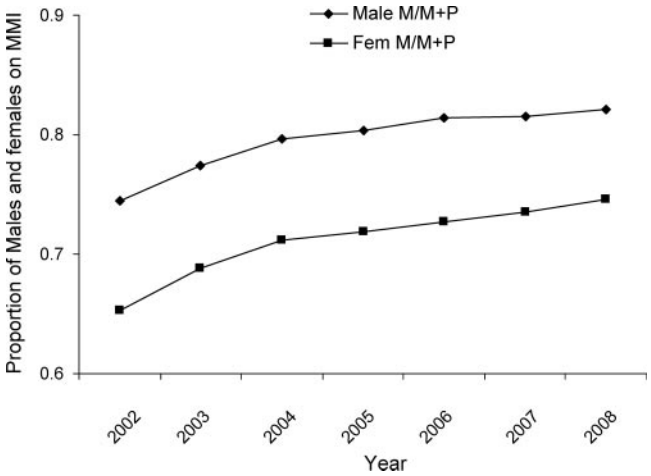

FIG. 2. Proportion of males and females taking antithyroid drugs who were using MMI from years 2002–2008, Surveillance Data, VONA database, extracted March 2009.

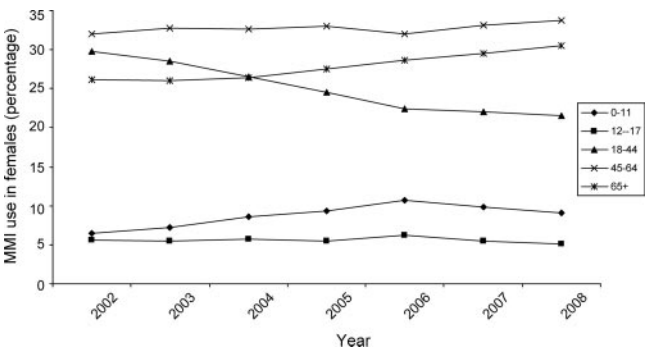

FIG. 3. Percentage of MMI use among females by age group from 2002 to 2008, Surveillance Data, VONA database, extracted March 2009.

TABLE 3. New patient prescriptions for PTU and MMI

	2005	2006	2007	2008
MMI total	144,025	135,144	140,299	148,776
Years				
0–11	15,756	18,010	18,311	17,714
12–17	8,821	9,613	9,887	9,907
18–44	45,122	38,873	40,402	41,801
45–64	45,349	40,909	43,749	47,864
65+	28,977	27,739	27,950	31,490
PTU total	46,988	43,496	42,513	41,551
Years				
0–11	366	325	297	313
12–17	995	765	775	756
18–44	22,750	20,687	20,350	19,808
45–64	14,093	13,160	13,097	12,847
65+	8,784	8,559	7,994	7,827

Data source was Surveillance Data, VONA, extracted April 2009.

ism. For this calculation, the total number of new PTU and MMI prescriptions per age group for year 2008 was divided by the projected 2008 census numbers for each age group (Table 3). For the 0- to 11-yr age group, the estimated incidence was 0.44 per 1000; in the 12- to 17-yr age group, the incidence was 0.26 per 1000; in the 18- to 44-yr age group, the incidence was 0.59 per 1000; for the 45- to 64-yr age group, the incidence was 0.78 per 1000; and for the 65+ yr age group, the estimated incidence was 1.01 per 1000.

Dispensed outpatient prescriptions by prescriber specialty

During 2008 endocrinologists accounted for approximately 30% of dispensed prescriptions for MMI, followed by internists with 20% and general practitioners, family medicine physicians, and doctors of osteopathy with 13%. Prescriptions written by pediatricians accounted for approximately 2% of dispensed prescriptions. For PTU, internists and endocrinologists each accounted for approximately 27%, followed by general practitioners, family medicine physicians, and doctors of osteopathy with 24%. Prescriptions written by pediatricians accounted for approximately 2% of dispensed prescriptions for PTU.

Discussion

The present study provides an overview of thionamide use in the United States over almost 2 decades, revealing important and heretofore undocumented trends in prescribing practices. Since 1996 MMI has become the most frequently prescribed thionamide, with an 800% increase in the number of dispensed outpatient prescriptions. On the other hand, the number of dispensed PTU prescriptions reached a plateau in the early 1990s, and its use rate remained virtually unchanged through 2008. The reason for this dramatic change in clinical practice is likely due to a combination of factors. First, the side effect profile favors MMI. Although agranulocytosis is a potential adverse effect of both thionamides, it is dose related for MMI and less so for PTU (15). PTU is the cause of rare but potentially life-threatening hepatotoxicity, whereas severe hepatotoxic reactions related to MMI are extraordinarily rare (12, 16, 17). Also, PTU is a far more common cause of ANCA-positive vasculitis than is MMI (18, 19). The more convenient dosing of MMI, translated into enhanced adherence, also makes it preferable to PTU. Finally, MMI is more effective than PTU in controlling severe hyperthyroidism (10). These advantages are unlikely to be anything more than a minor explanation for the change in prescribing practices because the differences in toxicity, adherence, and efficacy had been well known before the 1990s when PTU use still dominated the market.

Perhaps the most likely explanation for the dramatic rise in MMI prescribing is the availability of generic MMI in the late 1990s. Previously Tapazole was more expensive than PTU, but now the price of the two generic drugs is roughly similar at comparable effective doses (http://www.destinationrx.com/, accessed August 30, 2009). Finally, the number of case reports of PTU-induced severe liver toxicity more than doubled in the 1980s and 1990s compared with the previous decades (14). Whether this phenomenon is also linked to the changes in prescribing patterns for the thionamides remains unknown.

In our study, the only subgroup in which MMI use did not increase was in women of childbearing age. Indeed, MMI use actually decreased in this age group. This is in accord with the current recommendations contained in the Endocrine Society clinical practice guidelines for the man agement of thyroid disease in pregnancy (20), as well as a recent FDA alert (http://www.fda.gov/Drugs/ucm162701.htm), and an American Thyroid Association statement (21) for use of PTU as the first-line agent in the management of hyperthyroidism during pregnancy. Although The Endocrine Society's clinical guidelines were published in 2007, they reflected previous expert opinion (22), based on a literature linking the use of MMI during pregnancy to birth defects, including choanal atresia, aplasia cutis, and tracheal-esophageal fistulae (23). In the past, concerns about a greater transplacental transfer of MMI compared with PTU also led to MMI being avoided during pregnancy. However, recent studies showed that PTU is transplacentally transferred at a rate similar to MMI (24, 25). This knowledge may have led to declining use of MMI in pregnancy and in women who wish to become pregnant well before the publication of the guidelines and warnings in 2007 and 2009, respectively. Because the proportion of women using PTU in this age

group also decreased, it is possible that more women of child-bearing age are choosing radioiodine therapy before pregnancy.

The estimated incidence rates for hyperthyroidism estimated by new-to-therapy prescriptions for antithyroid drugs in 2008 may be a reasonable surrogate for the actual incidence in the American population. Because a large proportion, if not the vast majority, of patients who undergo radioiodine treatment or thyroidectomy for the management of hyperthyroidism are treated with an antithyroid drug at some point in their clinical course, it is likely that these patients have been captured by the databases used in this study. Furthermore, because more than 90% of patients below the age of 50 yr who present with hyperthyroidism have Graves' disease (26), the estimated incidence of hyperthyroidism presented in our study is indeed a surrogate for Graves' disease incidence in young to middle-aged individuals. Our rates are slightly higher than the incidence rates previously reported for Western societies. In Sweden, the annual incidence of hyperthyroidism in adults was estimated to be 0.33 per 1000, with an annual incidence of 0.51 and 0.14 per 1000, in females and males, respectively (26). A study performed in the United Kingdom reported an annual incidence of hyperthyroidism of 0.77 per 1000 in women and 0.14 per 1000 in men (27). Data from the Nurse's Health Study II indicated a much higher incidence of Graves' disease in women of 4.6 per 1000 (28).

A recent systematic review of the literature on the incidence of autoimmune thyroid disease estimated the incidence of hyperthyroidism to be 0.8 per 1000 in women and 0.08 per 1000 in men, which is surprisingly similar to the overall incidence we presently report of between 0.44 per 1000 in children and 1.01 per 1000 in the elderly (29). Unfortunately, we were unable to estimate incidence in relation to gender because the data on new prescriptions did not include sex distribution. On the other hand, we were able to estimate the incidence of hyperthyroidism in children. Our rates were higher than the previously reported U.S. incidence of 0.04 per 1000 in the population younger than 19 yr (30). Because most children are treated with antithyroid agents, this estimated incidence may be more accurate than the estimates for adults. The adult incidence of hyperthyroidism that we report in our study may be an underestimation because some patients who receive radioiodine are never treated with antithyroid drugs and would not be counted using our methodology.

The data presented in this study should be interpreted in the context of the known limitations of the databases used. For example, the databases provide the total number of prescriptions by age and gender only from 2002 to 2008 and not throughout the study period, which is from 1991 to 2008. Moreover, the database did not provide information on the gender of patients receiving new prescriptions. Finally, it is unclear why the total number of dispensed antithyroid drug prescriptions increased from a few hundred thousand in the early 1990s to more than a million in 2008. Because it is unlikely that the incidence of hyperthyroidism is increasing dramatically, given the relatively stable numbers of new prescriptions dispensed between 2005 and 2008 (Table 3), it is plausible that the remarkable increase in the number of dispensed thionamide prescriptions over the past 2 decades reflects a growing preference for long-term primary pharmacotherapy instead of radioiodine treatment. Whereas it is possible that the database did not capture prescriptions written in the 1990s as accurately as in more recent times, the methods for compiling drug sales by Surveillance Data Vector One has not changed over the study period (personal communication, Timothy McGee, associate director, Client Solutions, Syndicated Analytics at Surveillance Data).

It is certain that changes in antithyroid drug prescribing patterns will continue to occur. It is surprising that despite sound evidence concluding that PTU should be used in only certain circumstances and not as a first-line drug that approximately one quarter of new prescriptions for the treatment of hyperthyroidism in 2008 were for PTU. Hopefully, with the new FDA warning, this proportion will continue to fall in the coming years, as it has most dramatically in children. With regard to the treatment of hyperthyroidism during pregnancy, it is unclear how to balance the competing risks of rare MMI embryopathy and MMI-related aplasia cutis in the fetus with the very uncommon occurrence of PTU-related severe hepatotoxicity in the mother. Only future clinical and epidemiological studies will be able to answer this question.

Acknowledgments

Address all correspondence and requests for reprints to: David S. Cooper, M.D., Division of Endocrinology, Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 333, Baltimore, Maryland 21287. E-mail: dscooper@jhmi.edu.

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