A Study of Compliance With FDA Recommendations for Pemoline (Cylert®)

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ABSTRACT

Objective: To assess compliance with product labeling recommendations to use pemoline as second-line therapy for attention-deficit/hyperactivity disorder (ADHD) and to obtain baseline and biweekly liver enzyme tests. **Method:** Retrospective cohort study using administrative claims data to identify first-line therapies and liver enzyme tests among pemoline users between January 1, 1998, and March 31, 2000. Prescriptions for first-line therapy were searched for 90 days prior to the first pemoline claim. Liver enzyme testing (baseline and follow-up) was compared between two groups (the prerecommendation cohort October 1, 1998, to March 31, 1999, and the postrecommendation cohort October 1, 1999, to March 31, 2000). **Results:** 1,308 patients received at least one pemoline prescription during the study period; 76% of patients ≤20 years were male. ADHD was the claims-identified indication for 688 patients (52%). Despite the labeling recommendation for use as second-line therapy, only 237 ADHD patients (34%) received a first-line therapy prior to pemoline. Only 12% and 11% of the pre- and post-cohort patients, respectively, received baseline liver enzyme tests; 9% in the pre- and 12% in the post-cohort received at least one liver enzyme follow-up test. **Conclusions:** Compliance with product labeling was low for both recommendations. Understanding the reasons for this finding could help improve risk management strategies. *J. Am. Acad. Child Adolesc. Psychiatry*, 2002, 41(7):785–790. **Key Words:** attention-deficit/hyperactivity disorder, pemoline, labeling.

An estimated 4% to 12% of 6- to 12-year-olds in the United States have attention-deficit/hyperactivity disorder (ADHD) (Brown et al., 2001), and many of them will be treated with some type of psychotropic medication. Pemoline (Cylert®), one of the drugs available for the treatment of ADHD, was approved by the Food and Drug Administration (FDA) in 1975. At the time of approval, delayed hypersensitivity reactions involving the liver were noted to occur in 1% to 2% of patients receiving pemoline, leading to recommendations in the precautions section to monitor liver transaminase levels periodically. In the first year of U.S. marketing, one case of serious pemoline-related hepatotoxicity was reported to the FDA. Subsequently, reports of serious cases of pemoline-related hepatotoxicity appeared in the literature, including cases of acute liver failure (Adcock et al., 1998; Berkovitch et al., 1995; Elitsur, 1990; Hochman et al. 1998; Jaffe, 1989; Marotta and Roberts, 1998; McCurry and Cronquist, 1997; Nehra et al., 1990; Page et al., 1974; Patterson, 1984; Pratt and Dubois, 1990; Rosh et al., 1998; Safer et al., 2001; Sterling et al., 1996).

Continuing reports of liver toxicity prompted a labeling change in December 1996 that was accompanied by a "Dear Healthcare Provider" (HCP) letter to U.S. physicians. The risk of liver failure with pemoline use was highlighted in a black box warning, and the drug was shifted from first-line to second-line therapy for ADHD. Concern about liver failure risk with pemoline continued, and in June 1999 the labeling was modified again. New recommendations were added specifying baseline and biweekly serum alanine aminotransferase (ALT) monitoring. Another Dear HCP letter was distributed at that time.

Interest in the impact of the 1996 and 1999 labeling changes led to the implementation of a study to measure

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adherence to the labeling recommendations (1) that pemoline be used only as second-line therapy for ADHD and (2) that liver enzyme levels be monitored at baseline and biweekly intervals thereafter.

METHOD

The study used information from UnitedHealth Group, a national health care company including 43 health plans across the United States. A longitudinal administrative claims research database is maintained for approximately 3 million persons enrolled in 12 affiliated health plans in 10 geographically dispersed states across the United States. These plans are all independent practice association (IPA) models with open access to a wide network of providers, and they reflect general medical practice in the community. In this model, because physicians and facilities are typically reimbursed on a discounted fee-for-service basis and providers must file claims to receive payment, the data are generally complete. Data for all health care encounters and outpatient prescriptions are collected and organized into separate files for pharmacy claims, physician encounters, facility utilization, and health plan enrollment. These files can be linked by a unique encrypted patient identifier, protecting patient confidentiality.

The two labeling changes were analyzed in different cohorts of members, based on the period of observation. The use of pemoline as second-line therapy was analyzed among patients who received at least one prescription for pemoline at any time during a 27-month period from January 1998 through March 2000. To determine compliance with the second labeling change, rates of liver enzyme monitoring were evaluated and compared in two 6-month periods before and after the June 1999 labeling change recommending baseline and biweekly ALT monitoring. Users with a pemoline prescription dated between October 1998 and March 1999 were assigned to a pre–labeling-change cohort, and users with a pemoline prescription dated after the June 1999 recommendation, between October 1999 and March 2001, were assigned to a post–labeling-change cohort. Inasmuch as some patients take a drug holiday in the summer, the months of June through September were excluded from the analysis of compliance with liver enzyme testing. Hence the number of users in the pre- and post-liver enzyme labeling change cohorts is smaller than the number of users in the cohort used for analyzing second-line therapy use.

Users in all study cohorts had to have at least 90 days of continuous enrollment prior to the first pemoline prescription during the selected periods of observation (index claim). The definition of a course of therapy began with the date of the first prescription and continued with subsequent prescriptions until 90 days had elapsed without a new prescription. The 90 days of continuous prior enrollment requirement was specified to identify "new use" of pemoline during the study period and to allow searching for first-line therapy prescription claims and baseline liver enzyme test claims.

Adherence to second-line therapy recommendations for pemoline was evaluated in the 27-month study period by searching for prescriptions of first-line ADHD therapies (methylphenidate [Ritalin®], dextroamphetamine [Dexedrine®], dextroamphetamine/amphetamine [Adderall®], and methamphetamine [Desoxyn®]) for all patients during the 90-day period preceding the index pemoline prescription.

Baseline and biweekly follow-up liver enzyme testing was analyzed by using laboratory claims in the two 6-month cohorts (pre and post). Baseline testing was defined as a laboratory claim for serum liver enzyme testing from 30 days before through 7 days after the index prescription. Follow-up testing was defined as any laboratory claim for liver enzyme testing from 8 days after the index prescription through 8 days after the end of the last prescription period. Liver enzyme testing included laboratory codes for ALT, hepatic function panel, and multipanel clinical chemistry profiles.

Indication for pemoline therapy was obtained from physician claims submitted within 3 months prior to the date of the index pemoline prescription until the end of the study period. The primary *ICD-9* code for ADHD, 314.0, and comorbid conditions associated with ADHD (300.1, 307.2, 309.3, 309.4, 312, 314.2, and 315.0) were used to classify the indication as ADHD-related. Narcolepsy (347, 307.4) and multiple sclerosis (340) were included in the analysis as possible off-label indications.

Statistical analyses were completed with SAS version 6.12 (SAS Institute Inc., Cary, NC). Rates of first-line therapy use prior to pemoline and rates of baseline and follow-up liver function tests were calculated. Bivariate and multivariate analyses with χ^2 and logistic regression were carried out to analyze (1) the effects of age, gender, prescribing provider specialty, and indication on first-line therapy use; and (2) baseline and follow-up liver enzyme testing in pre- and post-cohorts.

RESULTS

There were 1,308 patients with an index pemoline prescription during the study period January 1998 through March 2000. Overall, 59% of pemoline users were male. Among patients ≤20 years of age, 76% were male, compared with 42% >20 years of age ($p < .0001$).

The median number of pemoline prescriptions was two. Thirty-six percent of patients had only one prescription and 52% received ≤60 days' supply of pemoline. The number of new users beginning therapy each month decreased from a high of 83 in March 1998 to a low of 19 in August 1999 (Fig. 1).

The primary indication among pemoline users was ADHD (Table 1); 688 (52%) of all users had this indication, and 493 (72%) of these were male. The primary prescribers for patients using pemoline were psychiatrists, family practitioners, neurologists, and pediatricians (Table 1).

Of the 688 patients receiving pemoline for ADHD, 237 (34%) received a first-line therapy prior to pemoline. Multivariate analyses showed that age, indication for use, and prescribing physician specialty were significantly associated with first-line therapy use. Younger ADHD patients (<20 years of age) were more likely to have received first-line therapy than older ADHD patients (odds ratio [OR] = 2.5, $p < .0001$), as were those with a first pemoline prescription from a pediatrician (OR = 1.7, $p < .03$) or psychiatrist (OR = 1.6, $p < .02$).

For the analysis of liver enzyme monitoring, 364 users were included in the pre-cohort (221 [61%] male, 197 [54%] ≤20 years of age) and 172 users in the post-cohort (94 [55%] male, 84 [49%] ≤20 years of age).

Overall, the liver enzyme testing rates did not differ between the two cohorts. Baseline liver enzyme testing

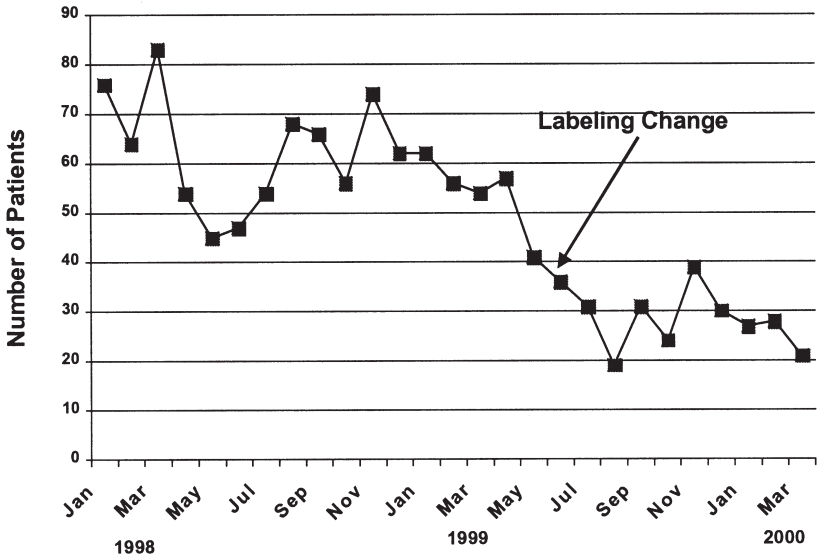

Fig. 1 Number of new users entering the cohort by month/year of index prescription, January 1, 1998–March 31, 2000.

rates were similar for the pre- and post-cohorts (12% and 11%, respectively) and did not differ by age (Table 2). The percentage of patients receiving any follow-up testing also was low for the pre- and post-cohorts (9% and 12%, respectively). Bivariate analysis found that the rate of at least one follow-up test among users in the 0–10 years age group increased in the post-cohort (5% versus 18%; $p < .05$). Multivariate analyses showed that the rate of both baseline and follow-up liver function testing did not differ significantly by age, gender, indication, or prescribing provider specialty, among both pre- and post-cohorts. Among patients with more than 4 weeks of use, few had evidence of obtaining biweekly liver enzyme tests (Table 3). Only seven patients from the pre-cohort and four from the post-cohort received more than one follow-up test.

DISCUSSION

This study found that labeling changes, including black-box warnings, had no measurable effect on compliance with the labeling recommendations for pemoline. Study results indicated that pemoline appeared to be used primarily as a first-line therapy for ADHD, with infrequent liver enzyme monitoring among all users. In fact, while labeling recommended biweekly enzyme monitoring, no one in this cohort of patients fulfilled this level of periodic follow-up testing. Regulatory efforts did

TABLE 1
Indications for Pemoline Use and Prescriber Specialties, January 1, 1998–March 31, 2000

	Age ≤20 yr (n = 634)	Age >20 yr (n = 674)	Total (N = 1,308)
Indication			
ADHD-related diagnosis	521 (82)	167 (25)	688 (52)
Narcolepsy	6 (1)	103 (15)	109 (8)
Multiple sclerosis	0	101 (15)	101 (8)
Others	107 (17)	303 (45)	410 (31)
Prescriber specialty			
Psychiatry	150 (24)	204 (30)	354 (27)
Family practice	182 (28)	99 (15)	281 (21)
Neurology	48 (8)	151 (23)	199 (15)
Pediatrics	159 (25)	13 (2)	172 (13)
Other	95 (15)	207 (30)	302 (23)

Note: Values represent no. (%). ADHD = attention-deficit/hyperactivity disorder.

TABLE 2
Number (%) of Users in Pre-Cohort and Post-Cohort Who Received Baseline and Follow-up Liver Enzyme Tests by Age Group

Age (yr)	Pre-Cohort (n = 364)		Post-Cohort (n = 172)	
	Baseline	Follow-up	Baseline	Follow-up
0–10	11 (13)	4 (5)	5 (15)	6 (18)
11–20	16 (15)	8 (7)	5 (10)	2 (4)
21–40	6 (8)	10 (13)	3 (7)	7 (17)
41 +	9 (10)	12 (14)	6 (13)	6 (13)
Total	42 (12)	34 (9)	19 (11)	21 (12)

TABLE 3
Number of Follow-up Liver Enzyme Tests by Days of Pemoline Prescription for Users in Pre-Cohort and Post-Cohort

Days of Pemoline Supply	No. of Follow-up Liver Enzyme Tests			
	0	1	2	≥3
1–27				
Pre (n = 31)	29	2	NA	NA
Post (n = 9)	9	0	NA	NA
28–55				
Pre (n = 139)	135	4	0	0
Post (n = 70)	67	3	0	0
>55				
Pre (n = 194)	166	21	5	2
Post (n = 93)	75	14	2	2
Total				
Pre (n = 364)	330	27	5	2
Post (n = 172)	151	17	2	2

Note: NA = not applicable.

not appear to succeed in impacting physician behavior or the manner of pemoline use, but they may have played a role in the decreased use of the drug, although it is possible that the decrease in use may also have been related to the reports of hepatotoxicity.

These findings are based on data from commercially insured as well as Medicaid populations drawn from several IPA model health plans affiliated with a large national health insurer (UnitedHealth Group) that is geographically diverse and represents general medical practice in the community. A review of the prescribing patterns of central nervous system stimulant medications (CNSS) among UnitedHealth Group patients younger than 20 years of age from six health plans showed that about 2% of CNS drug users received pemoline, 56% received methylphenidate, 13% received dextroamphetamine, and nearly 30% were prescribed dextroamphetamine/amphetamine in 1999 (Shatin and Drinkard, 2002). Prescribing patterns in this population were comparable with national rates of CNSS drug use. Data from the 1999 National Ambulatory Medical Care Survey found similar distribution of the four CNSS drugs among persons younger than 20 years (methylphenidate was most frequently mentioned in visits made to office-based physicians at 50%, followed by dextroamphetamine/amphetamine at 24%, dextroamphetamine at 20%, and pemoline at 6% [National Center for Health Statistics, 1999]). In addition, inasmuch as UnitedHealth Group does not have any disincentives for liver enzyme testing for patients, our estimates of liver enzyme testing are likely to be similar to those for other settings.

The findings from this study are consistent with the results from other studies showing that product labeling may not meaningfully affect physician behavior (Graham et al., 2001; Smalley et al., 2000; Walker et al., 1995). Walker et al. found that liver enzyme monitoring within the first 8 weeks of beginning therapy with nonsteroidal anti-inflammatory drugs was rarely performed, despite labeling recommendations. Cisapride, used for the treatment of nocturnal heartburn, was found to prolong QT intervals and cause torsade de pointes in some patients. Although multiple labeling changes, warning statements, and Dear HCP letters were issued, the use of cisapride in patients with underlying risk factors for torsade de pointes and those taking other medications that interfere with cisapride metabolism showed little change (Smalley et al., 2000). Another recent example concerns troglitazone, an antidiabetic agent found to be associated with development of acute liver failure (Graham et al., 2001). In a series of Dear HCP letters, the FDA and the drug manufacturer recommended progressively more intensive liver enzyme monitoring as a means of preventing this serious adverse reaction. An analysis correlating specific FDA regulatory actions with the performance of monitoring found that patients were inconsistently tested and that after 3 months of therapy, fewer than 5% of patients had received the complete series of recommended testing (Graham et al., 2001).

Reasons for noncompliance with labeling recommendations are unclear, particularly related to liver enzyme monitoring, where both patient and provider behavior

influence compliance. The health belief model describes those factors necessary for behavior change to occur and may help explain the findings (Rosenstock et al., 1988). Health behavior change requires (1) sufficient motivation to make the health issue relevant, (2) the belief that one (in this case the patient) is vulnerable to the health problem, and (3) the belief that the health recommendation will reduce the risk. One would assume that providers are motivated to prevent adverse drug events, such as acute hepatotoxicity, in their patients and thus the new labeling recommendations would be relevant. However, the other two factors in the model may be lacking. Given the relative rarity of severe liver injury with pemoline, providers are unlikely to have many past experiences with pemoline-induced hepatotoxicity and hence may believe that their patients are not at risk. In addition, providers may believe that liver enzyme monitoring will not prevent the event, particularly because all cases of liver failure reported thus far involved cumulative treatment of 6 months or longer. Inasmuch as many of the patients in this study received short treatment courses (<60 days), providers may again have thought their patients to be at low risk.

Limitations

This study of adherence to pemoline labeling has several limitations. First, the use of a 90-day window to determine previous first-line therapy at the time of the index prescription might have missed earlier treatment. However, a sensitivity analysis extending the time to identify the first-line prescription up to 180 days did not alter the study findings. The liver enzyme monitoring analysis was based on the days' supply of pemoline dispensed and may have differed from the actual number of days the drug was used by a patient. Given that 41% of patients among the pre- and post-cohorts received only one prescription of pemoline, it is possible that some patients did not receive more than 14 days of the drug and thus follow-up would not have been necessary. However, baseline liver enzyme testing should have been completed regardless of duration of use; these rates were extremely low, and the majority (59%) of patients who had more than one prescription should have had at least one follow-up test completed. Finally, the indication for pemoline prescribing was based on *ICD-9* codes from claims associated with the index prescription. Nearly one third of patients had some other indication that was not one of the known uses for pemoline. Without medical record validation, interpretation of the indication data must be done cautiously.

Clinical Implications

Although national data show that pemoline was used relatively rarely by patients younger than 20 years of age (National Center for Health Statistics, 1999) and our data showed that new users in our study population decreased from 1998 to 2000, a number of patients remain at risk for pemoline-related hepatotoxicity. The low level of compliance with labeling recommendations means that patients may experience a delay in the identification of pemoline-related hepatotoxicity, leading to potential serious health consequences for some patients, including liver failure. Inasmuch as elevated liver enzyme levels may not initially be associated with any symptoms, monitoring serves as an important safety procedure and should be included in the management plan for each pemoline-treated patient.

In summary, this study provides additional evidence regarding the ineffectiveness of labeling recommendations and Dear HCP letters. Research into the factors contributing to physician (and patient) noncompliance with drug safety warnings could prove useful in designing more effective risk management strategies.

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