

## Changes in Related Drug Class Utilization After Market Withdrawal of Cisapride

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**Background:** Recent Food and Drug Administration-mandated and company-initiated withdrawals of drug products from the marketplace have had an impact on utilization in related drug classes.

**Objective:** To investigate the impact of withdrawal of the prokinetic agent cisapride (Propulsid) on utilization of other gastrointestinal (GI) agents.

**Study Design:** A longitudinal, retrospective study using electronic prescription data from a state-funded geriatric prescription benefit program.

**Patients and Methods:** Prescription claims for 2644 patients using cisapride between January 10, 2000, and October 1, 2000, were analyzed with respect to points in time at which (1) prospective drug utilization review edits were implemented denying reimbursement of cisapride because of drug interactions, (2) the manufacturer announced its intent to cease production, and (3) the agent was withdrawn from the market. Prevalence of use, claims volume, and expenditures were compared for cisapride, proton pump inhibitors, histamine-2 receptor antagonists, and the prokinetic agent metoclopramide during these periods.

**Results:** Use of cisapride decreased precipitately even before implementation of a "medical exception only" reimbursement policy. After the change in policy, metoclopramide use increased, although this increase was not proportional to cisapride's decline. Although total GI expenditures declined within the cisapride cohort, this change had little impact on overall program GI expenditures.

**Conclusions:** The loss of cisapride did not significantly affect program-wide costs for GI drugs. However, the withdrawal of cisapride appears to have resulted in increased use of metoclopramide, a medication with a more serious adverse effect profile than cisapride. Further study is needed to evaluate the long-term clinical impact of such therapy changes.

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lar agents with less toxic side effect profiles.<sup>1-3</sup> Although withdrawal of these agents may serve the greater good by avoiding additional occurrences of life-threatening side effects, it also necessitates a practical reevaluation of stabilized drug therapy regimens for both the patient and physician.<sup>4</sup>

After its approval by the FDA in July 1993, the gastrointestinal (GI) prokinetic agent cisapride (Propulsid; Janssen Pharmaceutica Inc, Titusville, NJ) gained widespread acceptance as an effective addition to drugs available for the treatment of symptoms associated with gastroesophageal reflux disease (GERD) as well as, on an unlabeled basis, diabetic gastroparesis.<sup>5</sup> Beginning in 1998, however, a series of labeling revisions and enhanced warnings focusing on contraindicated concurrent disease states, drug interactions, and associated cardiac arrhythmias resulted in the March 2000 announcement that Janssen Pharmaceutica Inc would discontinue marketing the agent in the United States as of July 14, 2000.<sup>6-9</sup>

Previous studies have demonstrated that product withdrawals can have a significant impact on utilization in related drug classes as a result of the subsequent drug substitution.<sup>4</sup> The goal of the present study was to assess the impact of cisapride's withdrawal on utilization of other medications commonly associated with GERD therapy, and on program-wide and drug class-specific expenditures. Specifically, we sought to address the following questions: (1) How does market withdrawal of a highly utilized medication affect drug class-specific and overall program expenditures? (2) Does such a withdrawal motivate prescribers to make substantial changes to remaining drug regimens?

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In a recent 2-year period, 8 drugs have been withdrawn from pharmacy shelves because of a combination of Food and Drug Administration (FDA) and manufacturer concerns over dangerous side effects as well as, in some cases, availability of simi-

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To address these questions, we analyzed utilization and cost data for periods before and after implementation of prospective drug utilization review edits for cisapride by Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE). PACE is a state-funded prescription benefit program for Pennsylvania residents 65 years of age and older who meet predetermined income requirements. In 1999, the PACE program reimbursed dispensing pharmacies more than \$300 million for more than 9 million prescriptions on behalf of approximately 240,000 enrollees.<sup>10</sup> Overall, GI agents ranked second in 1999 among all therapeutic classes in terms of program expenditures and third with respect to total claims volume, with more than 36% of participating cardholders using 1 or more of these agents.<sup>10</sup> Among all medications dispensed in 1999, cisapride (10 mg) ranked 44th in expenditures, accounting for 23,398 prescriptions and approximately \$1.2 million.<sup>10</sup> Program-wide utilization of other drugs commonly used to treat GERD is noted in **Table 1**.<sup>10</sup>

As part of its ongoing utilization review process, PACE relies on prospective drug utilization review criteria that identify therapeutic issues of concern via the point-of-sale electronic claims submission process. These edits may trigger a denial of reimbursement or a request for additional information. In response to the expanded warnings issued for cisapride, PACE disseminated enhanced warning bulletins on March 24, 2000. After the subsequent announcement of impending market withdrawal, PACE implemented edits to deny all claims for cisapride effective April 10, 2000, providing reimburse-

ment only after approval of a physician-requested medical exception. After market withdrawal on July 14, 2000, all claims were denied reimbursement with no exception.

... PATIENTS AND METHODS ...

All PACE prescription claims for medications dispensed between January 10, 2000, and April 9, 2000, were screened to identify all PACE cardholders who were using cisapride prior to intervention (n = 2644 persons). Information was then gathered regarding all GI medication use by these patients during the entire study period (January 10, 2000, through October 1, 2000). For therapeutic class analyses, the claims data were linked with the Red Book file of drug attributes provided by Medical Economics Company (Montvale, NJ). In addition to pricing information, the Red Book file provides American Hospital Formulary Service therapeutic class codes for each National Drug Code. The measures for the present study included (1) cisapride utilization and program expenditures; (2) utilization and expenditures among former cisapride users for other GI agents including metoclopramide, proton pump inhibitors, and histamine-2 receptor antagonists; (3) average daily doses of cisapride and other GI agents within the cisapride cohort; and (4) overall program-wide per member per month (PMPM) costs for proton pump inhibitors, histamine-2 receptor antagonists, and a "miscellaneous GI" therapeutic subclass containing both metoclopramide and cisapride.

**Table 1.** Selected PACE Gastrointestinal Drug Utilization—Calendar Year 1999

Drug	Program Expenditure (\$)	Claims	Expenditure Rank	Claims Volume Rank
Omeprazole (20 mg)* (Prilosec; AstraZeneca LP, Wayne, PA)	8,676,422	75,334	1	6
Omeprazole (20 mg)* (Prilosec; AstraZeneca LP, Wayne, PA)	6,476,532	57,985	2	11
Lansoprazole (30 mg) (Prevacid; TAP Pharmaceuticals, Deerfield, IL)	4,604,150	46,368	4	24
Famotidine (20 mg) (Pepcid; Merck, West Point, PA)	4,281,934	71,572	6	7
Lansoprazole (15 mg) (Prevacid; TAP Pharmaceuticals, Deerfield, IL)	2,287,460	21,895	18	89
Nizatidine (150 mg) (Axid; Eli Lilly, Indianapolis, IN)	1,279,726	21,527	42	92
Cisapride (10 mg) (Propulsid; Janssen Pharmaceutica, Titusville, NJ)	1,258,425	23,398	44	78

Drugs listed were in the top 50 products by either volume or expenditure.

\*The Prilosec products listed have different labeler (manufacturer) codes (first 5 digits of the National Drug Code) and are therefore counted as separate products.

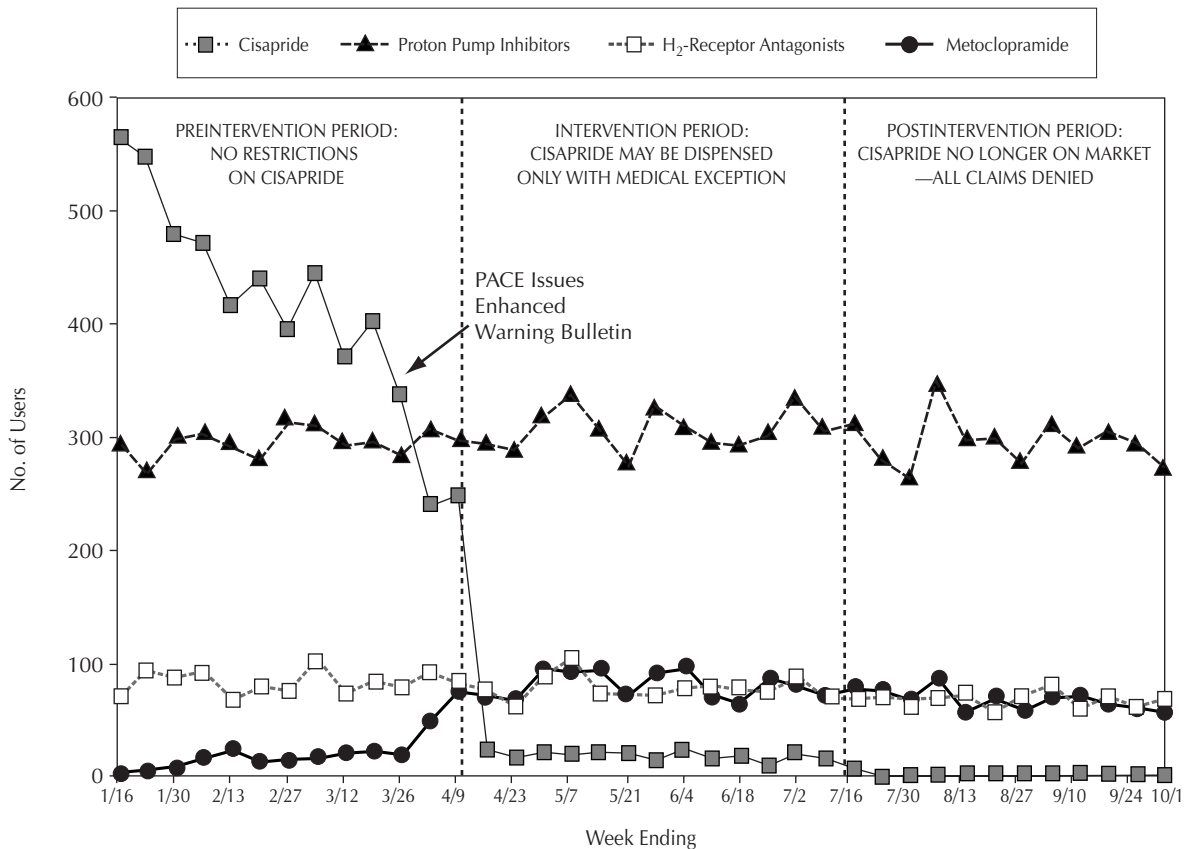
Total claims, expenditures, and number of users for each specific agent or GI drug class were evaluated for each week of the total study period. For additional analyses, which evaluated the impact of the cisapride intervention on use of other agents, the study period was divided into 3 equal intervals: (1) a preintervention time period of January 14, 2000, through April 9, 2000; (2) an intervention period of April 10, 2000, through July 6, 2000; and (3) a postintervention period defined (to maintain equal intervals) as July 7, 2000, through October 1, 2000. We used  $\chi^2$  tests to evaluate the significance of changes in prevalence of use of GI agents within the cohort of cisapride users. Changes in continuous measures of utilization, including total claims and expenditures, were evaluated for the cisapride users by means of repeated-measures analysis of variance (ANOVA). For these analyses of change, we omitted data on 180 cisapride users who withdrew from

PACE before the end of the study period, yielding an analytic sample of 2464 persons. Because the distributions of most of the utilization and expenditure variables were significantly skewed, these variables were log-transformed prior to conducting statistical tests on change.

... RESULTS ...

Of the total cohort of 2644 patients who were using cisapride before intervention, 2245 patients (84.9%) were women. The mean age of the cisapride cohort was 80.3 years (standard deviation 7.4 years, range 65–104 years). The study sample and the overall PACE population differed from the general elderly US population in that PACE cardholders were older on average and were more likely to be female. These demographic characteristics were

**Figure 1.** Utilization of Gastrointestinal (GI) Medications Within the Cohort of Former Cisapride Users



The number of persons within the cisapride cohort using each type of GI medication is shown by week (January 10, 2000–October 1, 2000).

largely the result of PACE's income limits, which resulted in a higher representation of very old, widowed women.

Figure 1 shows, on a weekly basis, the number of cardholders within the cisapride cohort who were dispensed cisapride, metoclopramide, proton pump inhibitors, and histamine-2 receptor antagonists over the course of the study. The data shown in Figure 1 suggest that use of cisapride declined substantially within the PACE program even before the program's institution of a "medical exception only" edit. Although a modest increase in use of metoclopramide can be seen after about March 26, 2000, no clear trends in the use of proton pump inhibitors or histamine-2 receptor antagonists are apparent.

Table 2 presents the results of  $\chi^2$  tests and repeated-measures ANOVA tests that were applied to evaluate the significance of changes in utilization within the cohort of cisapride users after program interven-

tions. Whereas 7.6% of cisapride users were using metoclopramide before the intervention, the proportion rose to 19.7% during the intervention period and then declined slightly to 16.4% during the postintervention period ( $\chi^2 = 156.9, df = 2, P < .0001$ ). No significant change occurred in the prevalence of use for histamine-2 receptor antagonists or proton pump inhibitors, although claims and expenditures for these agents declined slightly during the intervention and postintervention periods. The data shown in Table 2 also suggest that, despite the significantly increased use of metoclopramide, mean total GI claims and GI expenditures for the cohort of cisapride users declined significantly after intervention ( $P < .0001$  for both measures based on repeated-measures ANOVA).

Table 3 shows the mean daily dose for each GI agent during the preintervention, intervention, and postintervention periods. Results of ANOVA comparing mean doses for the 3 periods are also shown

**Table 2.** Changes in Use of Gastrointestinal Agents Among Cisapride Users

A. Prevalence of Use	Preintervention (%)	Intervention (%)	Postintervention (%)	$\chi^2$ Test		
				$\chi^2$	df	P
Cisapride	100.0	4.1	0.5*	6,912.88	2	< .0001
Metoclopramide	7.6	19.7	16.4	156.90	2	< .0001
H <sub>2</sub> -receptor antagonists	16.5	16.4	14.4	5.33	2	.0696
Proton pump inhibitors	53.9	55.4	53.4	2.08	2	.3529
Any of above	100.0	75.5	70.9	821.88	2	< .0001
Repeated-Measures ANOVA†						
B. No. of Claims	Preintervention (mean ± SD)	Intervention (mean ± SD)	Postintervention (mean ± SD)	F	df	P
Cisapride	1.88 ± 0.89	0.08 ± 0.42	0.00 ± 0.07*	19,878.50	2	< .0001
Metoclopramide	0.09 ± 0.36	0.39 ± 0.91	0.33 ± 0.85	192.57	2	< .0001
H <sub>2</sub> -receptor antagonists	0.38 ± 0.93	0.37 ± 0.93	0.32 ± 0.87	11.89	2	< .0001
Proton pump inhibitors	1.28 ± 1.32	1.40 ± 1.39	1.30 ± 1.34	16.05	2	< .0001
All of above	3.64 ± 1.77	2.24 ± 1.78	1.95 ± 1.66	1,753.93	2	< .0001
Repeated-Measures ANOVA†						
C. Total Expenditures	Preintervention (mean ± SD)	Intervention (mean ± SD)	Postintervention (mean ± SD)	F	df	P
Cisapride	\$120.53 ± \$83.63	\$5.76 ± \$37.08	\$0.38 ± \$6.12*	35,406.60	2	< .0001
Metoclopramide	\$1.21 ± \$5.19	\$4.87 ± \$12.62	\$4.25 ± \$12.23	160.49	2	< .0001
H <sub>2</sub> -receptor antagonists	\$20.49 ± \$55.60	\$19.91 ± \$55.18	\$18.47 ± \$54.66	7.02	2	.0009
Proton pump inhibitors	\$150.14 ± \$170.33	\$168.62 ± \$186.45	\$155.69 ± \$177.23	6.96	2	.0010
All of above	\$292.36 ± \$197.78	\$199.16 ± \$186.01	\$178.79 ± \$172.89	979.47	2	< .0001

n = 2464 persons who used cisapride prior to intervention and who did not withdraw from the PACE program at any time during the study. \*In order to maintain equal intervals, the period defined as "postintervention" for these statistical analyses included several days in which cisapride was still available through the medical exception process. A total of 12 individuals (0.5%) received cisapride during that time.

†Utilization and expenditure variables were log-transformed prior to repeated-measures ANOVA analysis.

for each agent. No statistically significant differences in dose between any of the times were found.

To obtain a broader picture of the impact of cisapride's withdrawal on overall program expenditures, program-wide PMPM costs for GI medications are shown in **Figure 2**. It should be noted that the PMPM values shown in Figure 2 reflect utilization by all GI medication users, not just utilization among former cisapride users. Despite the decline in cisapride use and the associated decrease in GI expenditures for the cisapride cohort, it is apparent from Figure 2 that overall program PMPM costs for GI medications actually increased during the study period.

... DISCUSSION ...

The pattern of decline in cisapride use before its withdrawal from the market suggests that many prescribers responded immediately to enhanced warnings about potential drug interactions. This decline is almost certainly a reflection of ongoing medical and lay press documentation of the FDA's and the manufacturer's increasing concerns regarding the parameters of use of cisapride. For those PACE cardholders remaining on cisapride at the time of the announcement of the pending market withdrawal, medical exception information obtained from physicians revealed that cisapride was more commonly used in conjunction with other agents as a treatment for GERD than as stand-alone therapy for gastropare-

sis. Based on this experience, it was not unreasonable to anticipate the possibility that prescribers would feel the need to add an alternative adjunctive agent or increase the dose of primary medication after cisapride was withdrawn from the market. However, neither of these presumptions appears to have occurred, with the average daily dose and total use of proton pump inhibitors and histamine-2 receptor antagonists remaining relatively stable. However, the use of metoclopramide increased significantly in proportion to preintervention metoclopramide utilization.

Although the expenditure data in Table 2 illustrate that the costs associated with new metoclopramide use did not outweigh the decline in expenditures associated with the removal of cisapride, it does not address the potential clinical implications of this increased metoclopramide use. The incidence of adverse reactions with metoclopramide use is significantly greater than with cisapride use, particularly in terms of central nervous system effects.<sup>11</sup> Extrapyramidal symptoms ranging from acute dystonic reactions to tardive dyskinesias, as well as Parkinsonlike symptoms, have been noted to increase in incidence from 0.2% to 9% with higher doses.<sup>11</sup> Central nervous system effects such as restlessness, drowsiness, fatigue, and dizziness have been observed in 12% to 24% of metoclopramide users.<sup>11,12</sup> Seizures and depression (ranging from mild to severe with suicidal ideation) have also been reported with metoclopramide use.<sup>11,12</sup> The more than 2-fold increase (7.6% to 16.4%) in metoclo-

**Table 3.** Changes in Mean Daily Dose for Gastrointestinal Agents

Drug Name	Preintervention Period		Intervention Period		Postintervention Period		Results of ANOVA		
	No. of Claims	Daily Dose, mg (mean ± SD)	No. of Claims	Daily Dose, mg (mean ± SD)	No. of Claims	Daily Dose, mg (mean ± SD)	F	df	P
Histamine-2 receptor antagonists									
Cimetidine	39	600.00 ± 254.43	44	656.82 ± 233.67	22	709.09 ± 290.99	1.36	2	.2621
Famotidine	371	29.60 ± 12.06	356	29.78 ± 11.57	306	30.72 ± 12.44	0.81	2	.4434
Ranitidine	380	218.62 ± 74.97	373	220.89 ± 77.27	336	219.01 ± 77.81	0.09	2	.9106
Nizatidine	144	206.61 ± 72.73	137	205.69 ± 72.61	126	224.81 ± 75.16	2.82	2	.0609
Proton pump inhibitors									
Omeprazole	1906	24.37 ± 9.01	2077	24.32 ± 8.91	1862	24.17 ± 9.07	0.27	2	.7631
Lansoprazole	1252	28.79 ± 11.15	1382	28.86 ± 11.26	1337	29.07 ± 11.61	0.22	2	.8003
Other agents									
Metoclopramide	232	26.41 ± 11.39	956	25.64 ± 11.71	803	25.52 ± 11.57	0.54	2	.5840

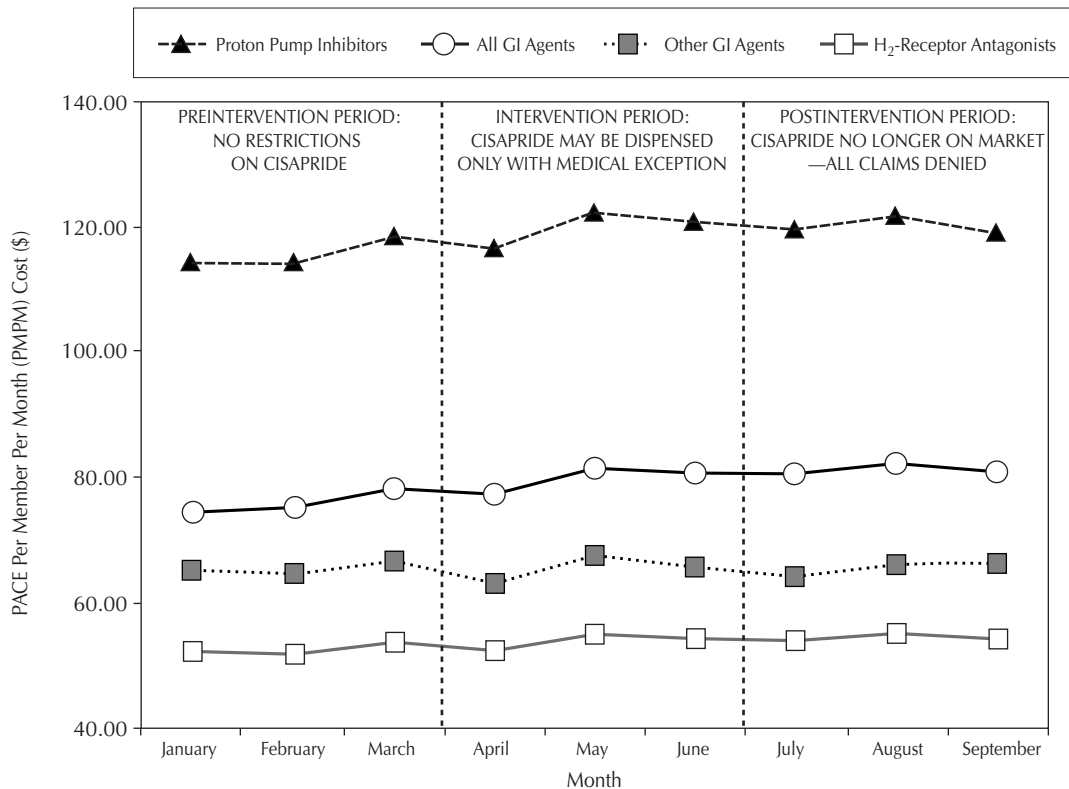
pramide use is a potentially alarming trend, particularly in an elderly population who possibly may already have a greater degree of central nervous system symptoms than younger patients. Therefore, metoclopramide use should be monitored to determine the long-term impact of this prescribing practice change on our elderly population. Further studies, including linkage to other medical data sources where possible, are needed to identify potential adverse outcomes associated with this shift to metoclopramide and to determine whether additional intervention is warranted.

Given that more than half of the cisapride users identified upon initiation of the study were also using a proton pump inhibitor at that time, PACE program staff anticipated the possibility of a significant increase in the number of proton pump inhibitor users or perhaps even an increase in the average daily dose of proton pump inhibitors. Neither of these scenarios appears to have taken place, however. A possible explanation for this lack

of change in concurrent proton pump inhibitor use is reevaluation of GERD therapy and the ability to maintain a proportion of patients symptom free using lower doses of proton pump inhibitors.

Although GI expenditures for the cisapride cohort declined significantly after the intervention, overall PACE program costs for all GI medication users increased. In an isolated environment, the loss of prescriptions for at least some of the 2644 cisapride users should theoretically have resulted in decreased costs to the program. However, in the broader scope of GI agents used by all members of the program, those 2644 cisapride users were greatly diluted, along with any potential cost savings, by the more than 41,000 PACE cardholders receiving some type of GI medication. Price changes are 1 potential factor driving expenditure increases. Because the PACE program updates its prescription pricing files on a monthly basis, it is subject to the impact of increasing drug costs on PMPM costs even over relatively short time periods. Examination of price changes for

**Figure 2.** Program-Wide Per Member Per Month (PMPM) Costs for Cardholders With Claims in Gastrointestinal (GI) Class



These PMPM values reflect total program-wide utilization, not just the utilization of former cisapride users.

all GI agents during the study period indicated increases for 2 proton pump inhibitors in February and March of 2000. Given the pattern of our results, it is possible that these increases contributed to the observed PMPM costs increases in the GI therapeutic drug class. It should also be noted, however, that the increased PMPM observed for GI agents was consistent with steady increases that were observed for overall program expenditures across all therapeutic classes. These increases reflect not only price changes, but also longitudinal utilization increases associated with increasing levels of illness in this elderly population. The level of comorbidity within the PACE program is high because of the high mean age of the participating population and issues related to adverse selection (ie, program participants tended to have greater levels of illness and medication needs than nonenrolled elderly). The mean number of broad therapeutic classes used by PACE cardholders on an annual basis was nearly 5 and the mean number of unique medications used during the course of 1 year was 8, reflecting the multiple comorbidities experienced by many elderly.<sup>10</sup> The high level of comorbidity in this elderly population not only contributed to program increases in expenditures, but also emphasizes the need for review and evaluation of all program changes affecting cardholders.

The present study has several important limitations. One limitation was the lack of extensive data on the indications for cisapride use in this population, because medical diagnoses were not readily available for the study sample. Diagnoses were available, however, for 225 patients whose physicians requested medical exceptions after the implementation of cisapride claim denial on April 10, 2000. Among patients whose physicians requested that their patients continue to receive cisapride, GERD was reported for 73% of patients and gastroparesis was named in 22% of patients. The remainder of requests cited dysphagia, Barrett's esophagitis, hiatal hernia, strictures, and erosive esophagitis as indications for use. Although these patients are not necessarily representative of all cisapride users, their reported diagnoses suggest that PACE cisapride users may have been 3 times as likely to be using this agent for GERD as opposed to gastroparesis. Epidemiological studies have reported prevalence rates of approximately 20% for weekly GERD symptoms,<sup>13</sup> and the prevalence of having GERD symptoms at least once monthly may be as high as 60% in elderly populations.<sup>13,14</sup> The prevalence of motility disorders has been noted in the literature as occurring in approximately 15% of surveyed populations

across all age groups<sup>15,16</sup>; however, Stanghellini<sup>16</sup> found that the proportion of those reporting symptoms of GERD increased significantly with age, whereas the proportion experiencing dysmotilitylike symptoms decreased significantly with age.<sup>16</sup>

A second limitation of the present study was the absence of a control or comparison group. Because the PACE intervention affected all cisapride users, no data are readily available that allow us to conclude that the observed utilization changes could be attributed definitively to the intervention, as opposed to other factors. For example, because of the nature of this benefit program, which serves only elderly patients, it is likely that some of the decline in utilization within the cisapride cohort reflected nonparticipation because of death or hospitalization. Although we were able to identify and exclude from analysis 180 cardholders who had disenrolled from the PACE program before the end of the study period, we did not have current data on hospitalization or mortality. For the remaining cisapride cohort, subsequent prescribing decisions could be affected by a number of clinical factors, such as the potential for reevaluation of intensity of therapy requirements (ie, acute vs maintenance dosing), possible contraindications or intolerable adverse reactions associated with alternative therapies, and cardholders' perceptions of alternative agent efficacy. However, the observed decline in utilization was sufficiently large to suggest that real decreases in GI agent utilization may have occurred among the cohort of former cisapride users. Possible explanations for this decrease in utilization include situations in which cardholders may have paid cash for cisapride during the intervention period and subsequently transferred to the Propulsid compassionate-use program after final market withdrawal. Given the brief time frame of this analysis it is also possible that final therapeutic adjustments have yet to be made for the cardholders in question. Of some concern is the possibility, which could not be examined in the present study, that some patients may have experienced recurrence of symptoms if no therapeutic alternative was prescribed after cisapride's removal. It is also possible that some cisapride users substituted over-the-counter medications or perhaps other products not normally classified as GI agents but which might be used in this context on an off-label basis (eg, erythromycin used to increase GI motility or the antiemetic peripheral dopamine antagonist agent, domperidone) after the intervention. However, given the level of communication with physicians that took place before and during

the intervention, we believe that adverse treatment effects should have been minimized. The fact that the decline in cisapride utilization began before any point-of-sale claim denials suggests an active reevaluation of therapy on the part of prescribers.

Finally, it should be noted that our study was limited in the types of outcome data that are presently available. The present report focused primarily on drug utilization and expenditure data, but program interventions and market withdrawals should also be evaluated based on medical outcome data and, where possible, data on quality of life. Data were not available on medical outcomes, such as physician visits, new diagnoses, or hospitalizations, nor on changes in patient symptoms or health-related quality of life after the intervention. Therefore, the present study should not be viewed as a comprehensive assessment of the effects of cisapride's withdrawal. Further studies to evaluate the impact of cisapride's withdrawal on health outcomes in this population and other populations are still needed.

In conclusion, we found that the loss of cisapride as a therapy option had both economic and clinical implications for the PACE program. In economic terms, despite loss of this therapy option, program-wide costs were not significantly reduced for GI agents, mainly because of the low numbers of cisapride users and concomitant increases in utilization and costs for some other GI agents by noncisapride users. Clinically, the withdrawal of cisapride appeared to have resulted in an increased use of metoclopramide, a medication with a more serious adverse effect profile than cisapride. Until further data on health outcomes associated with these changes in therapy become available, the final economic and clinical impact of cisapride market withdrawal remains to be seen and will need to be further evaluated.

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