

Intervention for decreasing excessive acetaminophen use in Pennsylvania Medicaid recipients

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About 2% of the U.S. population consumes an analgesic, antipyretic, or nonsteroidal antiinflammatory drug every day.¹ Acetaminophen is one of the most common ingredients in prescription and nonprescription medications. Currently, there are over 100 proprietary preparations of acetaminophen and over 200 proprietary multi-ingredient preparations containing acetaminophen.²

Acetaminophen is safe and effective in the treatment of mild to moderate pain.³⁻⁶ It is considered the drug of choice for patients with renal disease⁷ and the initial drug of choice by the American College of Rheumatology for patients with osteoarthritis.⁸ The American Medical Directors Association recommends acetaminophen as the initial analgesic for managing chronic noncancer pain in residents of long-term-care (LTC) facilities who have no liver disease or alcohol consumption.⁹ A drug-use evaluation conducted in four LTC facilities revealed that the four most frequently prescribed opioid analgesic products contained acetaminophen.¹⁰ That study found, furthermore, that 65% of all the LTC facility residents received acetaminophen and an opioid analgesic containing acetaminophen, putting them at risk for acetaminophen dose-related hepatotoxicity.

The generally recommended dosage of acetaminophen is no more than 4 g/day.^{6,11,12} Most patients can take this dosage without adverse effects.^{4,8,11,12} However, acetaminophen use can be associated with adverse effects, including anemia, asthma, rash, nephropathy, and impaired liver function.¹³ Factors increasing susceptibility to hepatotoxicity include chronic alcoholism, depletion of glutathione stores by malnutrition or chronic illness, and concomitant ingestion of cytochrome P-450 isoenzyme inducers.¹³ Serious or fatal hepatotoxicity has been reported after a moderate overdose or high therapeutic doses in alcoholics,^{5,12,14-17} fasting persons,^{16,18} and those receiving concurrent isoniazid, zidovudine, or barbiturate therapy.^{11,14} Hepatotoxicity has been reported in individuals without risk factors after short-term acetaminophen exposure, long-term

excessive acetaminophen exposure, and long-term therapeutic acetaminophen exposure.

Long-term acetaminophen use of greater than 4 g/day by those who seek pain relief and fever control may result in hepatotoxicity.⁴ Ostapowicz et al.¹⁹ found that 57% of patients with acetaminophen overdose had accidental toxicity that was defined as "many ingestions for pain relief without suicidal intent." A majority of the patients (83%) ingested more than 4 g of acetaminophen per day. The study suggests that many individuals may be unintentionally overdosing on acetaminophen. Barker et al.²⁰ described three cases of hepatotoxicity associated with the daily ingestion of 5-8 g of acetaminophen over several weeks.

In a study of acetaminophen use in the Ohio Medicaid population, about 3% of patients who filled at least six acetaminophen-containing prescriptions in a six-month period obtained greater than 4 g of acetaminophen per day, indicating chronic excessive use.²¹ The acetaminophen overusers received an average of 20 prescriptions containing acetaminophen during the six months. Many of the overusers had diagnoses suggesting liver problems. A majority of the prescrip-

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tions dispensed to the acetaminophen overusers were for combination products containing narcotics. Propoxyphene–acetaminophen combinations accounted for almost 50% of the acetaminophen-containing prescriptions.

Many acetaminophen-containing nonprescription products and all acetaminophen-containing prescription products are covered by the Pennsylvania fee-for-service (FFS) Medicaid program. Previous analyses of analgesic drug use in the Pennsylvania Medicaid program suggested overuse of acetaminophen. We conducted a claims-based drug-use review (DUR) to assess the effect of a physician-targeted educational intervention on excessive acetaminophen use in the Pennsylvania Medicaid population.

Methods. *Identification of high-dose acetaminophen recipients.* All paid prescription claims with a date of service between October 1, 2000, and March 31, 2001, for any acetaminophen-containing products were identified for each Pennsylvania FFS Medicaid beneficiary 21 years of age or older as of October 1, 2000. The average daily dose of acetaminophen for each recipient was calculated by dividing the total number of grams of dispensed acetaminophen by the duration of acetaminophen use in days. The number of grams of acetaminophen for each dispensed prescription was calculated by multiplying the quantity dispensed by the acetaminophen strength of the product. The duration of acetaminophen use (in days) was calculated by adding the number of days between the dispensing dates of the first and last prescriptions for acetaminophen-containing products to the number of days' supply of the last such prescription during the evaluation period. Recipients were considered high-dose users of acetaminophen if they had more than two acetaminophen prescription claims and the calculated average daily dose during acetaminophen

episodes exceeded 4 g during the six-month identification period.

Acetaminophen prescribers for these high-dose patients were then identified and mailed DUR educational packets, developed by the Pennsylvania Medical Society's Center for Professional Drug Education, on June 8, 2001. Each packet contained a personalized letter to the physician, patient prescription profiles, a list of commonly used prescription and nonprescription acetaminophen-containing products and the amount of acetaminophen per dose, a patient medication record, a physician response form, and a postage-paid return envelope. The letter focused on the potential problem of acetaminophen-induced hepatotoxicity and suggested that physicians adhere to generally recommended daily doses. The patient prescription profiles were intended to make the physicians aware of all the acetaminophen-containing products dispensed to their patients. The medication record form was to be distributed to patients so that they could record all the medicines they obtained, and the response form assessed physician willingness to modify patient drug therapy after the educational intervention.

Evaluation of intervention. The effectiveness of the intervention was evaluated in two ways. First, we examined changes in acetaminophen use among the cohort of high-dose patients. We assessed acetaminophen use in the same patients before the intervention, which allowed us to assess the impact of regression to the mean; that is, since we chose high-dose patients for the intervention, these recipients' acetaminophen use would have a tendency to decline regardless of any intervention. In addition, we selected a historical control group of high-dose patients for a period before selection of the intervention group and compared their acetaminophen use with that of the intervention group.

Second, we analyzed the entire FFS Medicaid population of acetaminophen users. We identified all acetaminophen users for periods before and after the intervention to assess the overall effect of the educational intervention on acetaminophen use. Patients were included in the analysis if they were eligible for FFS Medicaid benefits at the midpoint of the preintervention and postintervention periods.

For both the cohort and population analyses, we identified three measures of acetaminophen use: the mean number of acetaminophen claims per person, the mean daily dose of acetaminophen per person, and the proportion of persons with more than two acetaminophen claims and an average daily dose greater than 4 g. This last measure helped identify excessive use of acetaminophen and mimicked the measure used to identify high users included in the intervention.

The date-of-service range of October 1, 2000, to March 31, 2001 (the identification period), was used in identifying high-dose patients. For these patients, the preintervention evaluation period was December 1, 2000, to May 31, 2001, and the postintervention evaluation period was August 1, 2001, to January 31, 2002. To be included in the comparison of the preintervention and postintervention periods, patients had to be eligible for FFS Medicaid and prescription services at the midpoint of both periods. The identification period ended two months before the preintervention period because there was a lag of six weeks between prescription filling and availability of claims for analysis. If the identification period had been the same as the preintervention period, claims for prescriptions filled in May 2001 would not have been available until after the proposed intervention mailing date. The postintervention period began approximately two months after the

intervention mailing to allow an effect to occur. It would be unrealistic to attribute a change in acetaminophen use immediately after the intervention, since it would take time for physicians to react to the information. The same preintervention and postintervention date ranges were used in the analysis of the entire population of FFS acetaminophen users.

Statistical analysis included comparisons of proportions and means with chi-square and *t* tests, respectively, for the analysis of the intervention cohort and the historical control group. The a priori level of significance was set at <0.05. Since the second part of the evaluation included the entire Medicaid population of acetaminophen users, statistical significance was not computed.

Results. *Cohort analysis.* A total of 624 recipients were identified as high-dose users of acetaminophen, and 833 physicians were identified as prescribers of acetaminophen to these recipients. The number of physicians identified per recipient ranged from 1 to 13. Sixty percent of recipients had one acetaminophen prescriber, and 24% had two.

Table 1 summarizes the baseline characteristics of the intervention and historical control high-dose patients. Both groups had similar distributions by race and sex, but the control group was about two years older than the intervention group (*p* = 0.02). Of the 624 high-dose users identified for intervention, 14 (2.2%) were no longer receiving acetaminophen during the preintervention period, and only 400 (64.1%) were high-dose users during the preintervention period. That is, for some patients, high-dose use of acetaminophen occurred in the early part of the identification period (October and November 2000) and ceased before the preintervention period started in December 2000. That is, acetaminophen use declined for some of the high-dose users even before the intervention was implemented.

Table 1.

Demographic Characteristics of Patients Taking High Dosage of Acetaminophen

Characteristic	Intervention Group (n = 624)	Historical Control Group (n = 590)	<i>p</i> ^a
No. (%) female	382 (61.2)	355 (60.2)	0.71
Mean ± S.D. age (yr)	50.8 ± 14.9	53.0 ± 17.3	0.02
Race, no. (%)			
Caucasian	576 (93.7) ^b	557 (94.4)	0.58
Other	39 (6.3)	33 (5.6)	

^aChi-square test to compare proportions and *t* test to compare means.

^b*n* = 615; race could not be identified for nine subjects in the intervention group.

There were 523 high-dose users who were eligible for comparisons before and after the intervention. The average number of acetaminophen claims per person decreased from 13.3 to 9.3, the average daily dose of acetaminophen per person (during acetaminophen episodes) decreased from 4.62 g to 3.23 g, and the fraction of high-dose acetaminophen users decreased from 340/523 (65.0%) to 170/523 (32.5%) (*p* < 0.001 for all three comparisons).

Figures 1 and 2 illustrate that the high-dose users had high acetaminophen dosages for one year before the intervention and that their acetaminophen use was greatest in the period immediately before the intervention. Figures 1 and 2 also compare trends of acetaminophen use between the intervention cohort and the historical control group. Overall, the groups appeared to have similar trends of acetaminophen use during all time periods. Both groups appeared to have a similar decline in all three measures of acetaminophen use. However, the decline in the average number of acetaminophen prescription claims for the intervention group exceeded that for the control group by an average of one claim (*p* = 0.04). The decline in the average daily dose of acetaminophen was similar in both groups (1.4 versus 1.3 g for the intervention and control groups, respectively) (*p* = 0.6). Finally, there was a similar decline in the proportion of excessive users between the intervention and control groups (*p* = 0.84).

Population analysis. There were 61,986 FFS acetaminophen users in the preintervention period and 63,509 in the postintervention period. Acetaminophen users in the pre- and postintervention periods were primarily female (68.6% and 68.2%, respectively) and Caucasian (85.2% and 85.6%), and the mean age was 47.1 and 47.3 years, respectively. A small proportion had medical claims associated with a diagnosis of cancer (3.6% and 3.3%) or substance abuse (3.4% and 3.7%). There was a 9% decline in the proportion of high-dose acetaminophen users and no change in the other two measures of acetaminophen use (Table 2).

Physician willingness to alter therapy. One hundred twenty-three physicians (14.8%) responded to the original mailing of response forms to 833 physicians, and 164 physicians (19.7%) responded to the second mailing (sent to physicians who did not respond to the first mailing), for an overall response rate of 34.5%. Of the physicians who responded, 50% were willing to modify drug therapy for one or more patients, 30% were not willing to make any changes, and 20% did not respond to the question.

Discussion. DUR plays an essential role in assessing and improving prescription drug use and prescribing patterns. Many DUR programs use administrative claims databases to identify prescribing problems and to alert physicians about them.²² There are examples of both successful and unsuccessful controlled DUR pro-

Figure 1. Average number of acetaminophen claims and average daily dose in the intervention group (solid lines) and historical control group (dashed lines). The intervention-group periods occurred from June 1, 2000, through January 31, 2002. The historical control-group periods occurred from June 1, 1999, through January 31, 2001. The intervention occurred on June 8, 2001.

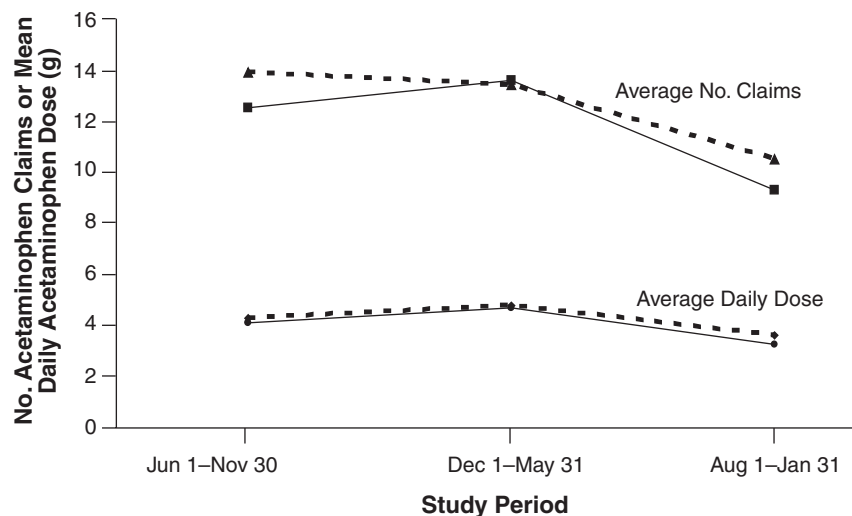
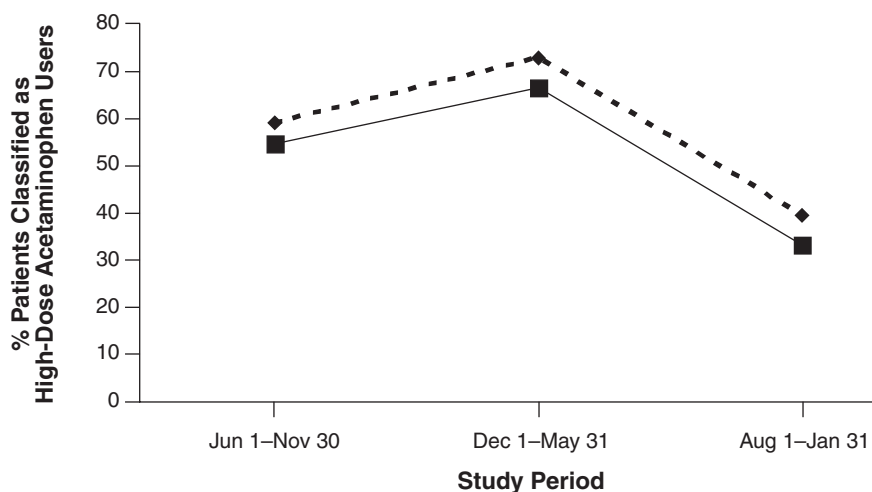


Figure 2. Prevalence of high-dose acetaminophen use in the intervention group (solid line) and historical control group (dashed line). The intervention-group periods occurred from June 1, 2000, through January 31, 2002. The historical control-group periods occurred from June 1, 1999, through January 31, 2001. The intervention occurred on June 8, 2001.



grams in which the impact of mailing printed materials on physician prescribing was assessed. In a study by Schaffner et al.,²³ Tennessee Medicaid data were used to select physicians prescribing four antibiotics. The authors found no significant difference in prescribing changes between the print-material group and the control group. In contrast, Zimmerman et al.²⁴ examined the impact of a DUR

letter on long-term prescribing of full-dose histamine H₂-receptor antagonists and found that the average monthly dose and antihistamine costs decreased significantly. Analysis of multiple studies indicates that DUR programs that combine educational materials with brief face-to-face visits by academic detailers are effective in improving prescribing practices.^{25,26}

Our DUR intervention resulted in a statistically significant reduction of acetaminophen overutilization in the intervention group. However, similar declining use of acetaminophen among the intervention and historical control groups suggests that the decline may have been due to factors other than the intervention alone. Regression to the mean may explain some of the observed decline in acetaminophen use in both groups. The physician survey indicated that most of the responding prescribers were willing to change their patients' drug therapy on the basis of the DUR mailing. However, the physician response rate was low, diminishing the reliability of that finding. Furthermore, we did not explore whether the physicians actually changed their prescribing practices.

Our study has several limitations. The historical control group may have differed from the intervention group in unmeasured characteristics. Although the use of a concurrent control group as well as random allocation would have been preferred, these features were not feasible in our study design, since all the targeted prescribers had to receive the intervention because of contractual obligations. Also, multiple nonintervention factors could have affected acetaminophen use in both the intervention and control groups. Finally, a reduction in excessive acetaminophen use may not necessarily mean a reduction in clinical outcomes, such as hepatotoxicity.^{25,27} Hennessy et al.²⁸ found no effectiveness of DUR in improving clinical outcomes, such as hospitalization due to all causes and cause-specific hospitalization.

Using administrative claims data to identify excessive use of drugs has several limitations. Prescription claims data suggest drug availability, but not whether the recipient actually took the drug or with what frequency. This is important when drugs are prescribed on an as-needed basis, as in the case of analgesics. To compen-

Table 2.
Acetaminophen Use among All Acetaminophen Users^a

Acetaminophen Utilization Category	Preintervention, Dec 1, 2000–May 31, 2001 (n = 61,986)	Postintervention, Aug 1, 2001–Jan 31, 2002 (n = 63,509)
Mean ± S.D. no. claims	3.3 ± 3.8	3.3 ± 3.8
Mean ± S.D. ADD ^b (g)	1.76 ± 1.4	1.76 ± 1.4
No. (%) pts. with >2 claims and ADD >4 g	607 (0.98)	563 (0.89)

^aPatients were included in the analysis if they were eligible for fee-for-service Medicaid benefits at the midpoint of each period.

^bADD = average daily dose.

sate for this limitation, we examined use over time and required more than two acetaminophen-containing prescriptions be dispensed. In addition, claims data do not include information on use of sample medications or nonprescription medications. Although the Pennsylvania FFS Medicaid program does pay for selected nonprescription medications, including acetaminophen, a recipient would have to have the physician write a prescription, which would probably require an office visit. Some recipients might prefer to pay out-of-pocket for the medication. This would tend to underestimate the number of recipients who are potentially at risk for acetaminophen hepatotoxicity. Heaton et al.²¹ suggested that uncaptured concomitant use of nonprescription drugs may underestimate acetaminophen use and thus the potential for hepatic toxicity. Overall, however, prescription claims do indicate drug availability and have been shown to be a reliable indicator of drug exposure.²⁹

Conclusion. An educational intervention aimed at prescribers was associated with a significant reduction of excessive acetaminophen use in patients who had been taking more than 4 g/day. However, similar declines in a historical control group suggested that other factors in addition to the intervention may have contributed to the reduction.

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