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Response to Propoxyphene Market Withdrawal: Analgesic Substitutes, Doses, and Adverse Events

Molly M. Jeffery, PhD,

Department of Health Sciences Research, Mayo Clinic, Rochester, MN

Nancy E. Morden, MD,

Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth College, Lebanon, NH;

Microsoft Artificial Intelligence and Research, Healthcare NeXT, Richmond, VA

Marc Larochelle, MD,

Section of General Internal Medicine, School of Medicine, Boston University, Boston, MA

Nilay D. Shah, PhD,

Department of Health Sciences Research, Mayo Clinic, Rochester, MN; OptumLabs, Cambridge, MA

W. Michael Hooten, MD,

Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, MN

Ellen Meara, PhD

Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth College, Lebanon, NH;

National Bureau of Economic Research, Cambridge, MA

Abstract

Objective—Experts cautioned that patients affected by the November 2010 withdrawal of the opioid analgesic propoxyphene might receive riskier prescriptions. To explore this, we compared drug receipt and outcomes among propoxyphene users before and after market withdrawal.

Study Design: Using OptumLabs data, we studied three populations: commercial, Medicare Advantage aged (**age 65+**) and Medicare Advantage disabled (**age <65**) enrollees. The exposed enrollees received propoxyphene in the 3 months before market withdrawal (n=13,622); historical controls (unexposed) received propoxyphene one year earlier (n=9,971). Regression models estimated daily milligrams morphine equivalent (MME), daily prescription acetaminophen dose, potentially toxic acetaminophen doses, non-opioid prescription analgesics receipt, emergency room visits, and diagnosed falls, motor vehicle accidents, and hip fractures.

Principal Findings: Aged Medicare Advantage enrollees illustrate the experience of all three populations examined. Following market withdrawal, propoxyphene users in the exposed cohort experienced an abrupt decline of 69% in average daily MME, compared to a 14% decline in the unexposed. Opioids were discontinued by 34% of the exposed cohort and 18% of the unexposed. Tramadol and hydrocodone were the most common opioids substituted for propoxyphene. The

Corresponding author: Molly M. Jeffery; jeffery.molly@mayo.edu; 612-227-2446 (cell); 200 First St SW, Rochester, MN 55905.

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proportion of each group receiving four or more grams of prescription acetaminophen per day decreased from 12% to 2% in the exposed group but increased from 6% to 8% among the unexposed. Adverse events were rare and not significantly different in exposed versus unexposed groups.

Conclusions: After propoxyphene market withdrawal, many individuals experienced abrupt discontinuation of opioids. Policymakers might consider supporting appropriate treatment transitions and monitoring response following drug withdrawals.

In November 2010, the opioid analgesic propoxyphene was withdrawn from the market for safety concerns.(1) Propoxyphene was a popular pain medication from 1957 until 2010.(2, 3) It was considered a weak opioid, prescribed for mild to moderate pain. Public Citizen, the consumer advocacy group, twice petitioned the US Food and Drug Administration (FDA) to withdraw it from the market—in 1978 and 2006—arguing the drug’s narrow therapeutic window may have contributed to accidental and intentional overdoses.(4) Evidence from clinical trials suggested propoxyphene added little analgesic effect to the acetaminophen typically combined with it.(5)

While one might expect the propoxyphene withdrawal to have reduced patient risk, the full impact of the policy depends on the risks of propoxyphene vs. those of substitutes chosen. Propoxyphene was on the Beers list of “potentially inappropriate drugs to be avoided in older adults.”(6) When the drug was withdrawn, the overall rate of inappropriate prescriptions among Medicare enrollees decreased 43%, largely because propoxyphene was no longer available. (7) Its withdrawal was also associated with a decrease in prescription opioid consumption among aged Medicare enrollees.(8) Despite these apparently positive developments, members of FDA advisory committees noted patients could face greater risk when switched to alternative drugs than they had faced from propoxyphene.(9) Prescribing changes prompted by propoxyphene market withdrawal may have put patients at risk for adverse outcomes in pain control, analgesic discontinuation-related adverse events, and possibly opioid-related adverse events resulting from more potent products.

Understanding the change in prescription drug use and health outcomes associated with this health policy should inform future prescription drug policies. To date, studies have not sufficiently explored the drug choice, dose and safety of substitutes propoxyphene users received after market withdrawal. **Existing studies have focused on population-level outcomes(10, 11) or included patients from a single healthcare system.**(12) No studies have examined post-withdrawal prescription drug use patterns in some important patient subgroups, including **aged** and disabled Medicare enrollees. Additionally, the impact of the policy on the use of acetaminophen, itself hazardous at high doses, has not been fully explored.

To understand changes in analgesic use and outcomes after propoxyphene withdrawal, we studied administrative claims data for three cohorts: **aged** Medicare Advantage, disabled Medicare Advantage (under age 65), and commercially insured adults. We explored opioid doses as well as post-withdrawal analgesic substitutes among former propoxyphene users. We estimated changes in opioid use, prescription acetaminophen use, non-opioid pain medication use, and health outcomes potentially associated with the adverse effects of

opioids, opioid withdrawal or pain: ED visits,(13) falls,(14) hip fractures, (15) motor vehicle accidents,(16) and opioid(17) or acetaminophen(18) poisonings/overdoses. Changes were compared to an unexposed control group of propoxyphene users from the year prior to market withdrawal. Collectively, these measures provide a detailed picture of prescriber and patient response to the policy and associated health outcomes.

Methods

Data and population:

This study used de-identified administrative claims data with linked socioeconomic status information from the OptumLabs® Data Warehouse (OLDW), which includes medical and pharmacy claims, laboratory results, and enrollment records for commercial and Medicare Advantage (MA) enrollees.(19) The database contains longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities and geographical regions across the United States.

To develop a comparison cohort as similar as possible to the cohort affected by the propoxyphene market withdrawal, we created two cohorts of propoxyphene users, one group exposed to the withdrawal of propoxyphene and the other a historical cohort not exposed to the withdrawal. The exposed and unexposed cohorts were identical except that the time frame for observation was one year earlier for the unexposed cohort than for the exposed cohort. To create the cohorts, we identified adults age 25 or older, continuously enrolled in MA or commercial insurance (medical and pharmacy) for the 18 months from March 2009 to August 2010 (unexposed, historic control cohort) or from March 2010 to August 2011 (exposed cohort). Propoxyphene users were defined as those with propoxyphene fills in two out of the three months from September to November of the index year. Individuals could be included in both the exposed and unexposed cohorts. See Figure S1 in Appendix for a cohort diagram.

We used administrative data to determine age, race/ethnicity, Census division of residence, household income, and insurance category (commercial, MA aged 65 and older, and disabled MA aged under 65). We used claims to identify Elixhauser comorbidities(20) and five additional comorbidities expected to impact risk of the health outcomes measured: tobacco exposure, serious mental illness, obesity/overweight, osteoporosis, and dementia. See Appendix for diagnosis codes used. Comorbidities were identified monthly on a rolling 6-month basis and required at least two outpatient or one inpatient record with one of the diagnosis codes.

Prescription claims were used to identify medications received including opioids and several prescription drug groups commonly used to treat pain (GABA analogs, tricyclic antidepressants, duloxetine, muscle relaxants, acetaminophen, and Non-Steroidal Anti-inflammatories). (21) See Appendix for details.

Opioid prescriptions were converted to milligrams morphine equivalents (MME); see Appendix. Days' supply was used to determine when a drug was available; total MME or mg acetaminophen received was used to calculate average daily dose for opioids and

acetaminophen (total MME or mg acetaminophen available in month/days in month). Dichotomous indicators were created for the other drugs of interest. Opioid and acetaminophen daily doses were top coded to minimize the impact of outliers, at 1000 MME and 6500 mg, respectively.

Primary outcome measures assessed by month included supply of opioid MMEs, mg prescription acetaminophen, and dichotomous variables indicating opioid discontinuation (0 MME in month), one or more days of potentially toxic acetaminophen doses (>4000 mg of prescribed acetaminophen available per day of acetaminophen use, among people with any prescribed acetaminophen), and/or one or more days of non-opioid pain medication.

Secondary measures included emergency department visits and rates of at least one health care encounter (inpatient or outpatient) with a diagnosis of hip fracture, fall, motor vehicle accident, opioid poisoning/overdose, or acetaminophen poisoning/overdose (see Appendix for codes used). Hip fractures were only assessed in the aged MA population.

Statistical Analysis:

To provide context, we described propoxyphene use in the total OLDW population with both medical and pharmacy coverage for at least one month between 9/1/2008 and 8/31/2009—a period before market withdrawal had been announced. We calculated the distribution of average daily doses by prescription for propoxyphene, hydrocodone, oxycodone, tramadol, and codeine.

Non-binary outcomes (i.e., opioid MME, mg acetaminophen, ED visits) were modeled with negative binomial models or truncated negative binomial models (when zeroes were excluded). Binary outcomes (any day with acetaminophen >4000 mg and any day with non-opioid pain medication) were modeled with logistic regression. The natural log of the number of days in the month was included in negative binomial models with the coefficient constrained to one in order to standardize across different month lengths. All models were specified with standard errors clustered on the beneficiary to account for repeated observations of individuals.

Covariates in main outcome models included all two-way and three-way interactions of cohort (exposed vs. historical unexposed) by month by beneficiary type (commercial vs. aged MA vs. disabled MA); sex; Census division; centered age and centered age squared (person's age minus mean age in sample); race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, and other); household income (categorical); and binary indicators for comorbidities. See Appendix for details. After modeling, adjusted predictions were calculated by beneficiary type, exposed/unexposed cohort, and month, holding constant the proportion of enrollees living in each census division, then plotted. Stata/MP 15.1 (22) was used for all analyses.

Adverse events including overdose/poisoning, motor vehicle accidents, falls, and hip fractures were analyzed differently because they were rare. We used a logistic regression at the patient level to model the odds of having at least one outcome diagnosis during the post-exposure period in the historical unexposed group vs. the exposed group. The independent

variable of interest was the cohort (exposed or historical unexposed). The only covariate included in the regression was beneficiary group (commercial, aged MA, disabled MA). The hip fracture analysis included only the aged MA group; it had no covariates.

Throughout the results, percentage changes were calculated using all decimal places and may differ slightly from calculations using the rounded results in the Appendix.

Results:

Summary results are presented here. Further details are in the Appendix including complete regression results.

Propoxyphene use before market withdrawal:

In the complete OLDW population with at least 1 month of medical and pharmacy coverage between 9/1/2008 and 8/31/2009, propoxyphene comprised 5.9% of the total opioid MME filled. In this period, propoxyphene was filled at a rate of 62, 90, and 168 fills per 1000 person-years by commercially insured, aged MA, and disabled MA enrollees, respectively. Oxycodone was filled at a rate of 138, 204, and 1,047 fills per 1000 person-years, and hydrocodone at a rate of 638, 610, and 2,029 fills per 1000 person-years for the three coverage groups, respectively. Figure 1 displays the distribution of dose for commonly used opioids. For weak opioids other than propoxyphene (codeine, hydrocodone, and tramadol), most prescriptions are 20 to 49 MME per day. The oxycodone dose distribution included more moderate to high doses. Propoxyphene's dose distribution mostly closely resembled oxycodone's. The modal propoxyphene dose was 90 to 119 MME per day.

Exposed and Unexposed Propoxyphene Recipient Cohorts:

We identified 6.1 million enrollees age 25 or older meeting insurance enrollment criteria. From this population, we identified 19,747 enrollees (283,116 total person-months) who met criteria for inclusion in one or both cohorts (exposed vs. historical unexposed); person-months were distributed between aged MA enrollees (31%), disabled MA enrollees (7%), and commercially insured enrollees (62%).

Table 1 provides descriptive statistics for the exposed and historical unexposed cohorts of propoxyphene users. The majority were white (ranging from 68% [disabled MA unexposed] to 80% [commercial exposed]). All nine census divisions were represented in the data, with the largest proportion coming from the South Atlantic region. Common comorbidities included hypertension, diabetes, and depression. See Appendix for a comparison of the OLDW population to the US insured population and for comorbidity prevalence.

Opioid use after propoxyphene withdrawal:

In comparison to the historical unexposed cohort, the exposed cohort showed a substantial decrease in the average daily MME (Figure 2a). In the aged MA group, adjusted daily dose decreased 69% from November to January for the exposed cohort and 14% in the unexposed cohort (see regression and margins in the Appendix). The commercial and disabled MA groups' results were similar, with a 61% MME decline in the exposed and a 15% MME

decline in the unexposed cohorts in the commercial group, and a 55% decline in the exposed and 9% decline in the unexposed disabled MA groups.

Two mechanisms contributed to the observed reductions in average daily dose: discontinuation of opioids and continued use at lower doses. Figure 3 depicts the proportions of the exposed and unexposed cohorts who received no opioids by month. The exposed cohort was more likely to discontinue opioids than the unexposed cohort. In the aged MA group, 34% (95% CI: 33% to 35%) of the exposed and 18% (95% CI: 16% to 20%) of the unexposed cohort received no opioids in January. In the commercial population, the proportions not using opioids in January were 36% (95% CI: 35% to 37%) of the exposed and 23% (95% CI: 22% to 24%) of the unexposed cohorts; in the disabled MA group, 24% (95% CI: 21% to 27%) of the exposed and 15% (95% CI: 12% to 19%) of the unexposed cohorts received no opioids in January.

Excluding those who discontinued opioids, the exposed cohorts' opioid dose (MME) declined 43% (disabled MA and commercial) and 56% (aged MA), while the unexposed cohorts' use remained largely unchanged (ranging from 2% decrease for aged MA to 3% increase for commercial).

In January, the most common treatment pattern across all three exposed cohorts was opioid discontinuation (no opioid fills). Among unexposed cohorts, continued propoxyphene use was the most common opioid treatment pattern for the two MA populations, while the commercial, unexposed group most commonly had no opioid fills.

Opioids prescribed after propoxyphene withdrawal:

Among exposed cohort members filling opioid prescriptions following propoxyphene withdrawal, the most common opioid received by aged MA enrollees was a low dose of tramadol (1 to 19 MME per day); for commercial and disabled MA enrollees, a low dose of hydrocodone (1 to 19 MME per day) was most common. In all three historical unexposed cohorts filling opioid prescriptions in the post-period, the most common drug was 20 to 49 MME of propoxyphene.

Prescription acetaminophen receipt after propoxyphene withdrawal:

After propoxyphene was withdrawn from the market, average daily prescription acetaminophen doses decreased by 65% (commercial), 67% (disabled MA) and 71% (aged MA) in the exposed cohorts and by 13% (aged and disabled MA) and 17% (commercial) in the unexposed cohorts (Figure 2b; full details in Appendix). The proportion of people receiving potentially toxic doses of prescription acetaminophen (>4000 mg per day) declined more in the exposed than the unexposed cohorts (Figure 2c): an 82% reduction in the aged MA and 83% reduction in the disabled MA cohorts and a 65% decline in the commercial cohort vs. a 14% decline in the unexposed commercial cohort and large relative increases in the unexposed MA cohorts (40% increase in the aged and 20% increase in the disabled cohort). Unexposed MA cohorts experienced a sharp decline in high doses of acetaminophen during the pre-period months (September to November), then stabilized at higher levels than the exposed cohort in the post-period. This pre-period decline was not observed in the exposed cohorts or in the unexposed commercial cohort. Unadjusted rates of

>4000 mg acetaminophen doses are plotted on a timeline in Appendix Figure S2, with reference to two FDA actions related to acetaminophen (see Discussion).

Other non-opioid medications:

We found no difference in receipt of non-opioid pain-related prescription medications: GABA analogs, tricyclic antidepressants, duloxetine, muscle relaxants, acetaminophen, and NSAIDs. (Figure 2d; details in the Appendix).

Adverse events:

We found no difference between the exposed and unexposed cohorts in the rate of emergency department visits in the post-period (Appendix Figure S3), nor in the prevalence of rare outcomes: opioid overdose, acetaminophen overdose, motor vehicle accident, fall, or hip fracture in the post-period (Table 2; full results in the Appendix).

Discussion

Following market withdrawal of propoxyphene, the rate of opioid discontinuation by propoxyphene users increased by 55% (disabled MA) to 87% (aged MA) compared to prior year cohorts. Among the exposed group who continued prescription opioids, the average dose fell by 43% (disabled MA and commercial) to 56% (aged MA). Historical unexposed populations did not experience these dose reductions. We also found dramatic reductions in the percent of enrollees receiving prescription acetaminophen at doses >4000 mg, a dose associated with liver toxicity. Despite substantially reduced prescription opioid use, however, we detected no statistically significant changes in ED visits or other rare adverse events following propoxyphene withdrawal.

During the study period, two regulation changes addressing the safety of acetaminophen were announced or took effect. A labelling change for over-the-counter acetaminophen products requiring warnings about the risk of liver injury was announced by the FDA in April 2009 to be implemented by April 2010.(23) In January 2011, the FDA announced a boxed warning on liver injury risk to prescription acetaminophen product labels and required withdrawal of prescription products with more than 325 mg of acetaminophen to be completed within 3 years. (24) The former change occurred during the unexposed cohort study period, while the latter occurred during the exposed cohort study period. These changes could explain some observed changes in acetaminophen use. The decline in >4000 mg prescription acetaminophen receipt predates the *implementation* of the over-the-counter labelling change by several months, though it may reflect the announcement in April 2009 of the regulation and findings of an FDA-convened advisory committee. The much larger decline in the exposed cohort predates the announcement of the prescription acetaminophen regulation and coincides with the withdrawal of propoxyphene from the market, suggesting the propoxyphene withdrawal was a major contributor to the decline.

Our results differ somewhat from prior studies examining the impact of the propoxyphene withdrawal in veterans (12) and a distinct commercially insured population (11). Hayes and colleagues found veterans affected by the propoxyphene withdrawal were 3 times more likely to discontinue opioids compared to a historical cohort of propoxyphene users, but the

absolute rate of discontinuation was only 10.6%--a much lower rate than seen in our study. The definition of discontinuation in the Hayes study was no opioids filled in the year after propoxyphene was discontinued. This was a more stringent definition of discontinuation than we used (30 days without opioids available); our definition reflects a common pattern of opioid use characterized by multiple distinct episodes of use separated by a month or more (25, 26).

Larochelle and colleagues (11) found that by two years after propoxyphene withdrawal and the reformulation of extended-release oxycodone, total MMEs filled had decreased by 19% in a commercially insured population. Larochelle and colleagues noted a “general lack of substitution” to other short-acting or long-acting opioids at the population level (i.e., not looking just at people taking propoxyphene). Our study explains these findings through large proportions of propoxyphene users discontinuing opioids or switching to **much lower doses of** alternative opioids.

The observed abrupt discontinuation of opioids does not appear aligned with recommended drug transition or opioid taper. Although voluntary tapering under medical supervision has been associated with reductions in pain and improvements in functioning,(27-29) recent clinical guidelines advise against abrupt discontinuation unless required for immediate safety concerns. (30) Chronic pain is associated with mental health conditions, particularly suicide.(31-33) Recent data suggest that clinician-initiated tapering may amplify the risk of suicidal ideation and self-directed violence.(34) Rapid, involuntary tapering may increase suffering, as patients experience withdrawal symptoms, untreated pain, functional decline, as well as a breach of trust with their clinician. (35, 36)

Experts often recommend reducing doses by 25% to 50% when switching patients from one opioid to another due to incomplete cross-tolerance. (37) This practice may partially explain the drop in MME in exposed cohorts; it does not explain discontinuation. Our data do not allow us to determine the appropriateness of individual treatment changes.

The observed prescription analgesic substitutions avoided risks from propoxyphene, but there are also risks from alternative drugs including tramadol and hydrocodone, the most commonly selected alternatives. Tramadol has a complex mechanism of action including serotonin and norepinephrine reuptake inhibition as well as a metabolite that acts as an opioid agonist. (38) In addition to opioid-related adverse events, tramadol is associated with increased seizure risk, serotonin syndrome, and hypoglycemia. (39-41) The risks of seizure and serotonin syndrome had been reported for at least 3 years prior to propoxyphene discontinuation.(42) At the time propoxyphene was discontinued, hydrocodone was a schedule III drug; hydrocodone has since been rescheduled to schedule II in recognition of its high abuse and addiction potential.(43)

The reduction in high acetaminophen doses is an underappreciated benefit of propoxyphene withdrawal. Potentially hazardous doses of prescription acetaminophen (>4000 mg) became much less common after propoxyphene was withdrawn. Propoxyphene combination products were prescribed with high doses of both propoxyphene and acetaminophen. The large share of individuals receiving prescriptions yielding such high doses of acetaminophen

highlights a risk of combination prescriptions that may warrant specific policy and practice interventions; common opioids including hydrocodone and oxycodone remain available as combination products. Though prescription acetaminophen products are now limited to 325 mg per tablet, patients remain at risk for overdose if they drink more than 3 alcoholic beverages per day or take multiple medications containing acetaminophen, including common over-the-counter cold, pain, and fever medicines.(44)

The lack of change in adverse event outcomes (ED visits, falls/hip fractures, car crashes), may suggest changes in drug receipt did not immediately translate into changes in these outcomes. Alternatively, it may reflect a heterogenous impact of this policy. Lower MME could *reduce* adverse events from overdose or side effects, while abrupt cessation of opioids could *increase* adverse events from opioid withdrawal or uncontrolled pain. These opposing effects may have led to the observed lack of change. Future research should explore potentially heterogenous effects of propoxyphene market withdrawal.

Although this study addresses a medication that was removed from the market nearly a decade ago, it provides important lessons to inform ongoing debates about opioid prescribing and the array of interventions available to address the ongoing public health crises of opioid overdose deaths. Policies aimed at restricting access to opioids may confer risks similar to those revealed in this analysis: dramatic dose changes without apparent tapering, substitutions to equally or more risky options, and perhaps most importantly, the possibility that patients' pain may no longer be treated. Regulation of drugs requires a complex assessment of risks and benefits to both individual and public health.(45) This study provides evidence that clinicians, pharmacists, and patients need guidance and access to alternative treatments when regulatory and policy changes affect drug availability.

Our study has several limitations. Most importantly, we do not directly measure important patient experiences including untreated pain and suffering. This is a limitation of claims-based analyses. However we do measure proxies for patient effects, including ED visits and falls. While prescription receipt has been demonstrated to be a good proxy for drug ingestion for other drug classes, no studies specifically measure the validity of prescription fills as a measure of drug use for opioids. The extent to which patients use prescriptions more quickly or slowly than intended or divert medication could affect our findings. Our outcome measures rely on accurate insurance claim coding to ascertain morbidities and adverse events. The measure of acetaminophen use includes prescription but not over-the-counter acetaminophen, which could understate total acetaminophen receipt. Finally, our findings may not be generalizable to Medicaid enrollees and the uninsured.

Conclusions

The potentially harmful sequelae associated with propoxyphene market withdrawal, including abrupt cessation of opioid use in one-quarter to one-third of propoxyphene users, reveal important policy challenges when harmful drugs are removed from the market. In discussions, FDA advisory committee members noted that they were uncomfortable advising the FDA on the risks of replacing propoxyphene with alternative products.(46) Policymakers should consider providing detailed recommendations from experts when drugs are

discontinued, rescheduled, or otherwise made less available. **Clinicians with patients affected by policy changes should work closely with their patients and with pharmacists to ensure that patients' preferences are followed and their needs are met by a new treatment regimen.** Monitoring policy-associated trends may also prove valuable and inform prompt refinement of recommendations in future cases of market withdrawal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Dose distribution for commonly prescribed opioids in population; all enrollees in source data with at least one month of medical and pharmacy coverage between September 2008 to August 2009

Figure 2:

Outcome trends in exposed and unexposed cohorts; adjusted predictions calculated adjusting for cohort (exposed vs. historical unexposed), beneficiary type (commercial vs. aged Medicare Advantage vs. disabled Medicare Advantage); sex; Census division; centered age and centered age squared; race/ethnicity; and comorbidities; vertical line indicates date of propoxyphene withdrawal in exposed cohort

Figure 2a: Opioid daily doses received before and after propoxyphene market withdrawal

Figure 2b: Prescription acetaminophen dispensed before and after propoxyphene market withdrawal

Figure 2c: Risk of one or more days exceeding 4000 mg of prescription acetaminophen

Figure 2d: Proportion of population receiving opioid-alternative prescription pain-related medications

Figure 3:

Proportion of cohort discontinuing opioids (no opioids available in month); adjusted predictions calculated adjusting for cohort (exposed vs. historical unexposed), beneficiary type (commercial vs. aged MA vs. disabled MA); sex; Census division; centered age and centered age squared; race/ethnicity; and comorbidities; vertical line indicates date of propoxyphene withdrawal in exposed cohort

Table 1:

Patient characteristics, opioid receipt, acetaminophen receipt

	Commercial		Patient Population				Disabled Medicare Advantage	
	2009 (unexposed)	2010 (exposed)	2009 (unexposed)	2010 (exposed)	2009 (unexposed)	2010 (exposed)	2009 (unexposed)	2010 (exposed)
N	7399	7139	2006	5298	566	1185		
Patient characteristics: N (%) except as noted								
Age (median [25th percentile, 75th percentile])	54.0 [46.0,60.0]	53.0 [46.0,59.0]	75.0 [70.0,80.0]	75.0 [70.0,81.0]	58.0 [52.0,61.0]	57.0 [53.0,62.0]		
Female	5,242 (70.8%)	5,037 (70.6%)	1,556 (77.6%)	4,004 (75.6%)	393 (69.4%)	835 (70.5%)		
Race/ethnicity								
White	5,875 (79.4%)	5,725 (80.2%)	1,443 (71.9%)	3,892 (73.5%)	386 (68.2%)	871 (73.5%)		
Black	937 (12.7%)	849 (11.9%)	397 (19.8%)	1,036 (19.6%)	131 (23.1%)	229 (19.3%)		
Hispanic	325 (4.4%)	336 (4.7%)	105 (5.2%)	219 (4.1%)	30 (5.3%)	56 (4.7%)		
Asian	71 (1.0%)	63 (0.9%)	17 (0.8%)	44 (0.8%)	-	11 (0.9%)		
Unknown/other	191 (2.6%)	166 (2.3%)	44 (2.2%)	107 (2.0%)	-	18 (1.5%)		
Census Division								
New England	85 (1.1%)	-	71 (3.5%)	139 (2.6%)	15 (2.7%)	32 (2.7%)		
Mid Atlantic	173 (2.3%)	159 (2.2%)	75 (3.7%)	117 (2.2%)	38 (6.7%)	55 (4.6%)		
East North Central	1,106 (14.9%)	1,068 (15.0%)	294 (14.7%)	881 (16.6%)	79 (14.0%)	175 (14.8%)		
West North Central	690 (9.3%)	690 (9.7%)	303 (15.1%)	655 (12.4%)	57 (10.1%)	129 (10.9%)		
South Atlantic	2,958 (40.0%)	2,702 (37.8%)	896 (44.7%)	2,514 (47.5%)	251 (44.3%)	554 (46.8%)		
East South Central	414 (5.6%)	352 (4.9%)	137 (6.8%)	617 (11.6%)	50 (8.8%)	152 (12.8%)		
West South Central	1,438 (19.4%)	1,501 (21.0%)	88 (4.4%)	113 (2.1%)	33 (5.8%)	32 (2.7%)		
Mountain	319 (4.3%)	346 (4.8%)	101 (5.0%)	180 (3.4%)	26 (4.6%)	40 (3.4%)		
Pacific	203 (2.7%)	221 (3.1%)	41 (2.0%)	82 (1.5%)	17 (3.0%)	16 (1.4%)		
Unknown	13 (0.2%)	-	-	-	-	-		
Household income								
Unknown	262 (3.5%)	225 (3.2%)	162 (8.1%)	258 (4.9%)	45 (8.0%)	61 (5.1%)		
<\$40K	1,238 (16.7%)	1,121 (15.7%)	1,229 (61.3%)	3,196 (60.3%)	310 (54.8%)	544 (45.9%)		

	Patient Population					
	Commercial		Aged Medicare Advantage		Disabled Medicare Advantage	
	2009 (unexposed)	2010 (exposed)	2009 (unexposed)	2010 (exposed)	2009 (unexposed)	2010 (exposed)
\$40K to \$49K	611 (8.3%)	560 (7.8%)	185 (9.2%)	536 (10.1%)	59 (10.4%)	137 (11.6%)
\$50K to \$59K	624 (8.4%)	620 (8.7%)	125 (6.2%)	379 (7.2%)	43 (7.6%)	109 (9.2%)
\$60K to \$74K	916 (12.4%)	929 (13.0%)	118 (5.9%)	346 (6.5%)	33 (5.8%)	127 (10.7%)
\$75K to \$99K	1,302 (17.6%)	1,306 (18.3%)	104 (5.2%)	321 (6.1%)	43 (7.6%)	108 (9.1%)
\$100K+	2,446 (33.1%)	2,378 (33.3%)	83 (4.1%)	262 (4.9%)	33 (5.8%)	99 (8.4%)
Selected comorbidities (most common; full set of comorbidities in Supplementary appendix)						
Cardiac arrhythmias	174 (2.4%)	144 (2.0%)	229 (11.4%)	537 (10.1%)	21 (3.7%)	64 (5.4%)
Hypertension (uncomplicated)	1,596 (21.6%)	1,495 (20.9%)	942 (47.0%)	2,454 (46.3%)	217 (38.3%)	429 (36.2%)
Chronic pulmonary disease	333 (4.5%)	314 (4.4%)	294 (14.7%)	613 (11.6%)	83 (14.7%)	180 (15.2%)
Diabetes (uncomplicated)	690 (9.3%)	652 (9.1%)	446 (22.2%)	1,091 (20.6%)	121 (21.4%)	265 (22.4%)
Rheumatoid arthritis/collagen vascular diseases	400 (5.4%)	346 (4.8%)	102 (5.1%)	227 (4.3%)	31 (5.5%)	70 (5.9%)
Depression	638 (8.6%)	593 (8.3%)	148 (7.4%)	287 (5.4%)	77 (13.6%)	174 (14.7%)
Opioid and Prescription Acetaminophen use (median [25th percentile, 75th percentile])						
Opioid daily dose (MME) pre-period *	29.0 [14.5,48.0]	29.0 [15.0,48.0]	30.0 [15.0,48.0]	30.0 [16.4,46.5]	37.5 [19.4,59.0]	37.5 [22.7,58.0]
Opioid daily dose (MME) post-period *	24.2 [2.4,46.5]	6.5 [0.0,17.7]	28.1 [8.7,46.3]	6.8 [0.0,15.0]	31.9 [12.5,55.7]	10.9 [0.0,24.0]
Rx APAP daily dose (mg) pre-period *	1174 [540,1975]	1216 [629,1973]	1300 [645,1974]	1258 [650,1950]	1364 [650,2167]	1387 [811,2232]
Rx APAP daily dose (mg) post-period *	987 [0,1907]	0 [0,833]	1170 [186,1929]	0 [0,729]	1258 [325,2097]	200 [0,1006]

- suppressed to preserve beneficiary anonymity

* Average dose per day, calculated over a month

Rx APAP= Prescription Acetaminophen

Table 2:

Association of propoxyphene withdrawal with diagnosed adverse events

Outcome	Odds ratio (95% CI)
Fall	1.11 (0.96,1.29)
Motor vehicle accident	1.34 (0.91,1.96)
Opioid overdose/poisoning	1.80 (0.90,3.59)
APAP overdose/poisoning	1.38 (0.54,3.53)
Hip fracture (aged MA only)	1.81 (0.94,3.48)

NOTE: Odds ratios for event during the post-intervention period for the exposed and historical unexposed cohorts were estimated using logistic regression controlling for beneficiary type (except hip fracture, analyzed only in the aged MA beneficiary group) APAP= Acetaminophen