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# Opioid-Paracetamol Prescription Patterns and Liver Dysfunction

## A Retrospective Cohort Study in a Population Served by a US Health Benefits Organization

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## Abstract

**Background:** Paracetamol (acetaminophen) is the most common cause of acute liver failure (ALF). ALF attributed to paracetamol is most often associated with the following features: an unintentional overdose, a single product, an opioid-paracetamol combination, duration of <7 days, and a median dose of 7.5 g/day. Currently, the recommended maximum daily dose of paracetamol is 4 g.

**Objectives:** The aims of the study were to determine opioid-paracetamol prescription patterns, including prescriptions exceeding the recommended dose of paracetamol (4 g/day) [prescriptions and beneficiaries]; examine factors associated with receiving opioid-paracetamol prescriptions in excess of paracetamol 4 g/day; and evaluate opioid-paracetamol prescription patterns for beneficiaries with liver dysfunction.

**Methods:** A retrospective cohort study examining prescription data of 4.8 million beneficiaries from a US health benefits organization from 1 January 2009 through 31 December 2009. The main outcomes examined were daily paracetamol dose and liver dysfunction.

**Results:** A large proportion (8.1%) of the 5.3 million prescriptions for opioid-paracetamol exceeded the recommended maximum daily dose of paracetamol (4 g/day), putting over one-quarter of a million (255 123 [18.9%]) of the 1.35 million beneficiaries receiving an opioid-paracetamol prescription at risk of toxicity. The most frequently prescribed products that exceeded paracetamol dose guidelines contained dextropropoxyphene and hydrocodone. Multiple factors, including type of product (i.e. dextropropoxyphene or oxycodone-containing), geographical location (Midwest), strength of the paracetamol in the opioid-paracetamol product (>325 mg) and prescriber specialty (dentist, physician assistant), were associated with high-dose paracetamol prescriptions. Liver dysfunction was diagnosed in 3818 cases, and 23.4% of these beneficiaries received an opioid-paracetamol prescription in the 90 days prior to the liver dysfunction diagnosis.

**Conclusions:** Although most opioid-paracetamol prescriptions are written and dispensed for <4 g/day of paracetamol, a significant portion of beneficiaries are being prescribed and dispensed excessive doses of paracetamol. Efforts to curtail this practice may involve provision of prescriber and pharmacist education, utilization of benefit manager systems to flag excessive dosing or that require confirmation of dosing, and implementation of US FDA recommendations supported by these data.

## Background

Every week, 23% of the US population take paracetamol (acetaminophen) in various forms, making it the most frequently used medication.[1] The popularity of paracetamol is due in part to its purported safety compared with other analgesics.[2-4] However, the Acute Liver Failure Study Group (ALFSG), who examined acute liver failure (ALF) in 22 academic centres over 6 years, found paracetamol accounted for 42% of all ALF cases in the US.[5] Cases of ALF attributable to paracetamol have increased over time from 28% in 1998 to 51% in 2003,[5] although values stabilized in 2004 and 2005 (52% and 46%, respectively).[3] While ALF is fairly rare (e.g. an estimated 1.4 cases per million people per year in Spain),[6] its mortality rate is 30% and therefore warrants vigilance.[3,7]

According to the ALFSG, most patients in the US who developed ALF associated with paracetamol do so unintentionally (48% unintentional, 44% intentional, 8% not determined).[5] Unintentional overdose is of concern because patients do not realize liver damage exists until they start to feel ill,[3] by which time severe damage has already occurred. This delay in identification of liver toxicity may partially explain the large role of unintentional paracetamol overdose in ALF.[5] The ALFSG found that ALF patients who had an unintentional paracetamol overdose, typically took an opioid-paracetamol product (63%), reported pain (81%) and used a single product (62%).[5] The median paracetamol dose for these patients was 7.5 g/day (range 1.0–78 g/day) and they rarely used paracetamol for more than 7 days.[5] This suggests that high-dose therapy, for even a short duration, can cause liver toxicity. Only a small proportion of ALF cases due to paracetamol (10%) appear to occur at dosages <4 g/day.[3] Therefore an opportunity exists to avoid paracetamol toxicity caused by unintentional overdose by identifying and targeting those patient characteristics associated with prescribing practices of >4 g/day of paracetamol.[3,5]

In June 2009, the US FDA convened an Advisory Committee to examine the issue of liver toxicity associated with paracetamol use.[8] The committee provided recommendations to decrease unintentional paracetamol overdose, including public education, label changes, daily dose limits (3.25 g/day), single tablet limits (325 mg immediate-release), single dose limits (650 mg) and removal of opioid-paracetamol products.[8] Subsequently, in January 2011 the FDA released a 3-year plan to limit the amount of paracetamol in opioid-paracetamol products to 325 mg per tablet and required labelling revisions regarding the risk for severe liver damage.[9]

A pilot study was undertaken in the Medicaid population of a rural Midwestern state to evaluate opioid-paracetamol prescribing practices that put patients at risk for unintentional paracetamol-related ALF.[10] Opioid-paracetamol products were the focus of the study because the majority of unintentional paracetamol overdoses causing ALF were due to an opioid-paracetamol product.[5] Results in the Midwestern state showed nearly one-quarter (23.3%) of the opioid-paracetamol prescriptions were written for more than 4 g of paracetamol, and dextropropoxyphene/paracetamol products had the highest percentage of prescriptions exceeding 4 g/day (49.1%).[10]

To ascertain the status of the opioid-paracetamol prescribing/dispensing patterns in the US and to answer questions prompted by the results of the Medicaid study, the current study was undertaken in a large health benefits company setting. The specific objectives of the study were to (i) determine opioid-paracetamol prescription patterns, including prescriptions exceeding the recommended daily dose of paracetamol (4 g/day) [prescriptions and beneficiaries]; (ii) examine the factors associated with beneficiaries receiving prescriptions for opioid-paracetamol in excess of paracetamol 4 g/day; and (iii) evaluate opioid-paracetamol prescription patterns for beneficiaries with liver dysfunction.

## Methods

### Study Design, Setting and Participants

This was a retrospective cohort study using Humana, Inc., pharmacy and/or medical claims data captured between 1 January 2009 and 31 December 2009. Beneficiaries aged between 18 and 89 years with at least one opioid-paracetamol prescription in 2009 and healthcare coverage through the government and/or a private insurance company (i.e. Medicare Advantage Prescription Drug [MA-PD] or Prescription Drug Plans [PDP], or fully-insured commercial) were included in this study. The MA-PD plan is for beneficiaries aged 65 years or older, some disabled people under 65 years of age and people of all ages with end-stage renal disease who receive both medical and prescription drug coverage from the health benefits organization. Beneficiary criteria for the PDP plan are the same as the MA-PD plan but beneficiaries only receive prescription coverage. The fully-insured commercial plan is for employer groups and individuals who pay a premium to the health benefits organization for both medical and prescription drug coverage. Use of over-the-counter (OTC) paracetamol medications by beneficiaries was not examined since the focus of this study was opioid-paracetamol use, and OTC data was not available to the health benefits organization. However, use of OTC paracetamol products in combination with opioid-paracetamol products could increase the risk of liver toxicity.

No liquid formulations of opioid-paracetamol prescriptions were included in the data because of difficulties determining the daily dose prescribed.

### Outcome Measures

The outcome measures used in the analysis included the following:

1. Mean daily dose of paracetamol for a single opioid-paracetamol prescription. This was calculated as shown in equation 1:

$$\frac{\text{Paracetamol content of drug} \times \text{quantity dispensed}}{\text{No. of days supplied by the prescription}}$$

2. Liver dysfunction. This was identified from medical claims based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and *International Classification of Diseases, Tenth Revision* (ICD-10) codes[11] that have been shown to be highly predictive for identifying paracetamol-related liver injury (sensitivity 93%, specificity 85%, C statistic –0.89).[12] These codes include hepatic necrosis 570, K71.1; toxic hepatitis 573.3, K71.2, K71.6, K71.9; and hepatic encephalopathy 572.2, K72.0, K72.9.[12] A diagnosis of liver dysfunction was counted only once per plan beneficiary.

### Co-Variates

The types of opioid-paracetamol prescription medications included in the analysis were hydrocodone/paracetamol, codeine/butalbital/paracetamol, codeine/paracetamol, dextropropoxyphene/paracetamol, oxycodone/paracetamol and dihydrocodeine/caffeine/paracetamol. The opioid-paracetamol combination medications contained paracetamol in various strengths (i.e. 300 mg, 325 mg, 356.4 mg, 400 mg, 500 mg, 650 mg, 660 mg, 712.8 mg and 750 mg). Sociodemographic information of each individual, such as age (at the time of prescription), sex, whether they received low-income subsidies, geographical location (Northeast, Midwest, Southeast, Southwest and West), and long-term care (LTC) facility residence, were also identified. Prescribers were categorized

as primary care physicians, dentists, physician assistants, nurse practitioners or all other prescribers.

### Data Analysis

Descriptive analysis of the sample population was carried out for all outcome measures except liver dysfunction. The number and percentage of prescription claims in 2009 for each type of opioid-paracetamol medication was examined. The total number and percentage of opioid-paracetamol prescription claims across three strata for average daily doses of paracetamol (≤3.25 g/day, 3.26–4 g/day, >4 g/day) was identified.

Multiple logistic regression analysis was used to examine factors associated with single opioid-paracetamol prescriptions written for >4 g/day. The unit of analysis was a single opioid-paracetamol prescription written for an MA-PD beneficiary, and the dependent variable was whether a single opioid-paracetamol prescription was written for an average daily dose of paracetamol >4 g/day. Independent variables included beneficiaries' age, sex, geographical location, low-income subsidy status, LTC facility residency, prescriber's specialty, type of the opioid-paracetamol prescription and strength of paracetamol in the opioid-paracetamol prescription. Members with missing information on independent variables were excluded from this analysis and totalled <0.5% of the study population.

For regression analysis, the three groups (MA-PD, PDP and fully-insured commercial) were analyzed separately because of the potential demographic differences among the three populations and the extremely large size of the sample in each group. The MA-PD regression results were chosen for publication because the MA-PD database was most robust and was used in analysis for liver dysfunction. In addition, the regression results were similar for the factors that were available in all three groups.

To examine liver dysfunction and prior opioid-paracetamol prescriptions, the sample population only included fully-insured commercial or MA-PD beneficiaries, as a diagnosis was only available for these two groups. Beneficiaries in this analysis also had liver dysfunction reported in 2009, were continuously enrolled in the plan 90 days prior to liver dysfunction (so as to capture beneficiaries who received a prescription for a 90-day opioid-paracetamol supply), and were between 18 and 89 years of age. Beneficiaries with pre-existing liver disease were not excluded from the study because of data limitations. Pharmacy claims data were then searched for the 90 days prior to the liver dysfunction event to examine opioid-paracetamol prescriptions. The 90-day period was chosen to capture beneficiaries receiving a 90-day supply of the opioid-paracetamol prescription. Only the opioid-paracetamol prescription closest to the liver dysfunction event was used to determine the average daily dose of paracetamol (which was categorized into three strata [≤3.25 g/day, 3.26–4 g/day, >4 g/day]).

Statistical significance was assessed at $\alpha = 0.05$. Adjusted odds ratios (OR), parameter estimates and 95% confidence intervals were obtained. The fit of the model was assessed using C and pseudo-R statistics. All independent variables except age were coded as a dummy variable. All statistical analyses were analyzed using SAS Enterprise Guide® (SAS Institute Inc., Cary, NC, USA).

Since the unit of analysis was a single opioid-paracetamol prescription, and a beneficiary could potentially contribute more than one observation in the logistic regression analysis, we conducted regression analysis through a generalized linear model with a binomial distribution and logit link, while the generalized estimation equation (GEE) method was used to account for the correlation among prescriptions from a single member. The results were similar to that of the logistic regression (GEE results not reported).[13]

The project was approved by the South Dakota State University Institutional Review Board and the appropriate Humana, Inc., internal review committee.

## Results

The records of 4.8 million individuals, enrolled in one of three healthcare insurance plan types (i.e. PDP, fully-insured commercial and MA-PD) during 2009, were examined for opioid-paracetamol prescriptions (table I). 1 351 905 beneficiaries (28.5%

**Table I.** Demographic characteristics of healthcare insurance beneficiaries

| Beneficiary population | MA-PD | PDP | Commercial | Total |
|---|---|---|---|---|
| **No. of beneficiaries** | 1.4 million | 2 million | 1.4 million | 4.8 million |
| Age [y; mean (SD)] | 72.2 (15.1) | 74.7 (15.9) | 35.5 (27.4) | NA |
| Female sex [n (%)] | 795 189 (55.8) | 1 210 806 (62.1) | 694 569 (50.8) | NA |
| **Opioid/paracetamol beneficiaries [n (% of total)]** | 468 437 | 628 779 | 254 689 | 1 351 905 (28.5) |
| Age [y; mean (SD)] | 68.5 (10.9) | 70.7 (11.3) | 43.1 (13.0) | NA |
| Female sex [n (%)] | 270 756 (57.8) | 396 760 (63.1) | 144 918 (56.9) | NA |

**MA-PD** = Medicare Advantage Prescription Drug plan; **PDP** = Prescription Drug Plan; **NA** = not applicable.

of all those examined) received a total of 5 300 688 opioid-paracetamol prescriptions.

The majority of prescriptions were for hydrocodone/paracetamol and dextropropoxyphene/paracetamol; these products were also prescribed most often at paracetamol dosages >4 g/day (table II). Evaluation of each individual opioid-paracetamol prescription claims across different average daily doses of paracetamol (i.e. ≤3.25 g/day, 3.26–4 g/day or >4 g/day) showed that most prescriptions had an average daily dose ≤3.25 g/day (n = 4 200 515; 79.2% of 5.3 million prescriptions). The number of prescriptions for paracetamol 3.26–4 g/day (n = 669 545; 12.6% of 5.3 million prescriptions) and paracetamol >4 g/day (n = 430 628; 8.1% of 5.3 million prescriptions) were much smaller.

When the frequency of beneficiaries prescribed opioid-paracetamol was examined across three paracetamol daily dose strata, most beneficiaries received a paracetamol prescription in the dose range of ≤3.25 g/day (n = 1 091 050; 80.7% of 1.35 million beneficiaries), while fewer beneficiaries had a prescription in the dose range of 3.26–4 g/day (n = 331 397; 24.5% of 1.35 million beneficiaries) and >4 g/day (n = 255 123; 18.9% of 1.35 million beneficiaries).

Multiple logistic regression analysis of the MAPD group showed the following were strongly associated with receiving a single opioid-paracetamol prescription >4 g/day: age, strength of paracetamol in the opioid-paracetamol prescription (356.4 mg and 712.8 mg paracetamol, 500 mg paracetamol, 650 mg paracetamol, 660 mg paracetamol and 750 mg paracetamol), receiving an opioid-paracetamol prescription from a dentist, nurse practitioner, physician assistant or providers other than a primary care physician, being male, and residing in the Midwest (table III). Compared with hydrocodone/paracetamol, products that presented the greatest risk for prescribing paracetamol >4 g/day were dextropropoxyphene/paracetamol (OR 1.606; 95% CI 1.560, 1.655) and oxycodone/paracetamol (OR 1.583; 95% CI 1.545, 1.623); codeine/paracetamol was not significantly different from hydrocodone/paracetamol

**Table II.** Prescription claims and healthcare insurance beneficiaries receiving each type of opioid/paracetamol combination in 2009

| Type of opioid/paracetamol combination | No. of prescriptions [n (%)] | No. of beneficiaries [n (%)][a,b] | No. of paracetamol prescriptions >4 g/day [n (%)] |
|---|---|---|---|
| Hydrocodone/paracetamol | 3 337 502 (62.96) | 917 669 (67.88) | 277 149 (8.3) |
| Dextropropoxyphene/paracetamol | 867 345(16.36) | 317 139 (23.46) | 97 048 (11.2) |
| Oxycodone/paracetamol | 839 945 (15.85) | 289 000 (21.38) | 49 630 (5.9) |
| Codeine/paracetamol | 243 151 (4.59) | 115 693 (8.56) | 6 517 (2.7) |
| Codeine/butalbital/paracetamol | 11 156 (0.21) | 2 497 (0.19) | 284 (2.2) |
| Dihydrocodeine/caffeine/paracetamol | 1 589 (0.03) | 598 (0.04) | |
| Total | 5 300 688 | 1 351 905 | 430 628 (8.1) |

a A beneficiary was counted more than once if more than one type of opioid/paracetamol prescription was dispensed.

b Percentages may not add up to 100%.

**Table III.** Factors associated with single opioid/paracetamol prescriptions >4 g/day in the Medicare Advantage Prescription Drug (MA-PD) plan population (n = 1 892 574)

| Variable | Number of Prescriptions >4 g/day | Adjusted OR (95% CI) | p-Value |
|---|---|---|---|
| **Age (y)** | 127 359 | 1.008 (1.007, 1.009) | <0.001 |
| **Sex** | | | |
| Female | 75 284 | Reference group | |
| Male | 52 075 | 1.027 (1.015, 1.039) | <0.001 |
| **Geographic location** | | | |
| Southeast[a] | 60 949 | Reference group | |
| Midwest[b] | 38 416 | 2.087 (2.058, 2.116) | <0.001 |
| Northeast[c] | 2 593 | 1.537 (1.474, 1.604) | <0.001 |
| Southwest[d] | 15 629 | 1.633 (1.602, 1.664) | <0.001 |
| West[e] | 9 772 | 1.648 (1.611, 1.687) | <0.001 |
| **LIS status** | | | |
| Non-LIS | 93 678 | Reference group | |
| LIS | 33 681 | 0.804 (0.793, 0.815) | <0.001 |
| **Prescription originated from an LTC facility** | | | |
| Not from an LTC facility | 123 818 | Reference group | |
| From an LTC facility | 3 541 | 2.475 (2.384, 2.570) | <0.001 |
| **Type of opioid/paracetamol prescription** | | | |
| Hydrocodone/paracetamol | 81 988 | Reference group | |
| Codeine/butalbital/paracetamol and dihydrocodeine/caffeine/paracetamol | 91 | 0.407 (0.306, 0.541) | <0.001 |
| Codeine/paracetamol | 1 645 | 1.117 (0.359, 3.473) | 0.85 |
| Dextropropoxyphene/paracetamol | 28 153 | 1.606 (1.560, 1.655) | <0.001 |
| Oxycodone/paracetamol | 15 482 | 1.583 (1.545, 1.623) | <0.001 |
| **Strength of paracetamol in the opioid/paracetamol medication (mg)** | | | |
| 325 | 17 782 | Reference group | |
| 356.4 and 712.8[f] | 90 | 17.743 (13.023, 24.173) | <0.001 |
| 300 | 1 648 | 0.663 (0.213, 2.061) | 0.48 |
| 500 | 54 711 | 2.760 (2.695, 2.826) | <0.001 |
| 650 | 34 114 | 2.630 (2.549, 2.713) | <0.001 |
| 660 | 476 | 1.830 (1.664, 2.013) | <0.001 |
| 750 | 18 538 | 8.627 (8.388, 8.873) | <0.001 |
| **Prescriber specialty** | | | |
| Primary care physician | 51 095 | Reference group | |
| Dentist | 6 293 | 3.295 (3.201, 3.392) | <0.001 |
| Nurse practitioner | 2 611 | 1.402 (1.346, 1.461) | <0.001 |
| Physician assistant | 3 807 | 3.268 (3.227, 3.309) | <0.001 |
| Others | 63 553 | 2.343 (2.262, 2.427) | <0.001 |

a Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, West Virginia and Virginia.

b Wisconsin, Michigan, Illinois, Indiana, Ohio, North Dakota, South Dakota, Nebraska, Kansas, Minnesota, Iowa and Missouri.

c Connecticut, Massachusetts, Pennsylvania, Delaware, New Hampshire, Rhode Island, Maryland, New Jersey, Vermont, Maine and New York.

d Arizona, Oklahoma, New Mexico and Texas.

e Alaska, California, Colorado, Hawaii, Idaho, Montana, Nevada, Oregon, Utah, Washington and Wyoming.

f Dihydrocodeine/caffeine/paracetamol.

**LIS** = Low-income subsidy; **LTC** = Long-term care; **OR** = odds ratio.

(OR 1.117; 95% CI 0.359, 3.473) [table III]. The predictive ability of the model had a C statistic of 0.725, and Pseudo-R statistics of 0.04 with the maximum rescaled R-square value of 0.104. The overall logistic regression model was significant at the 5% level, as indicated by the likelihood ratio, and Wald and Score tests (all $p < 0.0001$).

There were 3818 beneficiaries from the MA-PD and fully-insured commercial groups who had a reported liver dysfunction event. Of these individuals, 23.4% (894 of the 3818 beneficiaries with dysfunction) had received an opioid-paracetamol prescription within 90 days of the event. The distribution of patients based on the paracetamol dosage is shown in table IV. Only the paracetamol prescription closest to the liver dysfunction event was used to determine the average daily dose of paracetamol.

**Table IV.** Average daily dose of paracetamol in the opioid/paracetamol combination prescribed within 90 days of hepatotoxicity

| Average daily dose (g)[a] | No. of beneficiaries |
|---|---|
| <3.25 | 670 |
| 3.26–4.0 | 121 |
| >4.0 | 103 |
| **Total** | **894** |

a Only the paracetamol prescription closest to the hepatotoxicity event was used to determine the average daily dose of paracetamol.

## Discussion

This study found that a large proportion (28.5%) of a US-based population identified within a health benefits organization in 2009 received an opioid-paracetamol product, most often containing hydrocodone followed by dextropropoxyphene, oxycodone and codeine. The observed distribution of all types of opioid-paracetamol products is similar to that seen in Medicaid beneficiaries in a Midwestern state, although codeine products constituted a much smaller proportion in this study (17.0% in the Midwestern state vs 4.6% in this study).[10] In addition, the prominence of hydrocodone/paracetamol products as the most frequently prescribed opioid-paracetamol product is in line with hydrocodone's ranking as the most commonly prescribed product in the US and number one opioid-paracetamol prescribed in emergency departments.[14,15]

Paracetamol as the most common cause of ALF[5,7,16] is of serious concern, especially as most cases (48–61%) involve an unintentional overdose.[5,16] In addition, opioid-paracetamol medications warrant extra attention since they are the most common products involved in these unintentional overdose cases (63%).[5]

In our study, the majority (79.2%) of opioid-paracetamol prescriptions were written for equal to or less than the US FDA Advisory Committee's recommended dose of 3.25 g/day[8] and were filled by 80.7% of the beneficiaries receiving an opioid-paracetamol prescription. Furthermore, paracetamol doses exceeding the recommended 4 g/day[17] constituted 8.1% of the 5.3 million opioid-paracetamol prescriptions, but were prescribed to nearly one-fifth of the 1.35 million beneficiaries receiving opioid-paracetamol prescriptions (18.9%) who were therefore at greater risk for toxicity.

The 8.1% of paracetamol prescriptions in our study that exceeded 4 g/day is similar to the 5.9% reported in a recent study of California's Medicaid fee-for-service population,[18] but is less than the 23.3% reported in a Medicaid population in a Midwestern state.[10] This discrepancy may be due to differences in the population sampled, geographical location (the Midwest region was more likely than the Southeast region to prescribe paracetamol >4 g/day in our study) and frequency of opioid-paracetamol products prescribed.[10] Results from our study and the literature[19,20] suggest that multiple variables may affect prescription patterns (e.g. patient population, location).

The descriptive analysis (table II) showed a similar pattern to the Midwestern state Medicaid population where prescriptions of dextropropoxyphene and hydrocodone-containing opioid-paracetamol combinations contained paracetamol >4 g/day more often than codeine-containing combinations.[10] This information may be used to focus interventions that are most effective in improving prescribing and dispensing (e.g. focusing more on propoxyphene- rather than

codeine-containing combinations). It should be pointed out that the FDA recommended that dextropropoxyphene/paracetamol be voluntarily withdrawn from the US market in November 2010.[21]

The study data also showed high-strength paracetamol products (i.e. paracetamol 500 mg per tablet or more) are more likely to be prescribed at >4 g/day (OR 1.830; 95% CI 1.664, 2.013 to OR 8.627; 95% CI 8.388, 8.873 compared with paracetamol 325 mg), which is similar to the findings in the Midwestern state where eight high-strength paracetamol products were most often prescribed for >4 g/day (range of 23.9% to 100% of prescriptions).[10] The increased risk of prescribing more than 4 g/day of paracetamol found with higher strength products supports the FDA's plan to limit the single tablet strength to 325 mg.[9]

In order to determine prescribing practices, prescriber type was evaluated. It was found that dentists and physicians assistants tended to prescribe paracetamol >4 g/day more often compared with primary care physicians (OR 3.295; 95% CI 3.201, 3.392 and OR 3.268, 95% CI 3.227, 3.309, respectively). Literature examining physician characteristics associated with potentially inappropriate medication (PIM) prescribing has shown that in the ambulatory setting, non-physician prescribers are more than 3-fold more likely to prescribe a PIM than physicians.[19] Researchers have suggested that prescriber attitude and patient demands may influence inappropriate prescribing.[22] Special focus may be directed to these prescribers to help decrease excessive paracetamol dosing through approaches such as educational efforts (e.g. mailings, educational sessions).

Geographical location was associated with being prescribed an excessive daily dose of paracetamol (>4 g/day); this was less likely to occur in the Southeast region of the US and more likely in the Midwest. It is not clear why there are geographical variations in the prescribing of opioid-paracetamol prescriptions; however, a study of an ambulatory care population between 1995 and 2000 showed that patients in the South had a higher risk for PIM prescribing compared to the West.[20] Also, a study utilizing ambulatory care data from 1996 found that the Midwest and the South had an increased risk of PIM prescribing.[23]

Our study showed that residents of an LTC facility were more likely to receive a prescription for paracetamol >4 g/day compared with beneficiaries not living in an LTC facility (OR 2.475; 95% CI 2.384, 2.570). Research examining PIM prescribing rates similarly found high rates in LTC settings.[22,24] PIM prescribing in LTC settings has been attributed in part to the greater number of medications taken by residents.[22]

Patients' lack of knowledge about paracetamol-associated risks may also contribute to the overuse of opioid-paracetamol products. A recent study found that only one-third of patients know the maximum dose of paracetamol.[25] Therefore, if prescription directions do not contain daily maximum doses, in most instances the patient will not identify excessive use.

Larson et al.[5] and Bower et al.[16] examined ALF and identified paracetamol as the most common drug-related cause of ALF (42% and 41%, respectively). In addition, Larson et al.[5] found opioid-paracetamol combinations accounted for 15.9% of all ALF cases. In this study, there were 3818 cases of liver dysfunction diagnosed during the year and nearly one-quarter of these beneficiaries (894 of 3818) received an opioid-paracetamol prescription in the 90 days prior to the liver dysfunction diagnosis.[5] While the percentage of beneficiaries with liver dysfunction taking opioid-paracetamol was higher in this study than the percentage of ALF due to opioid-paracetamol found by Larson et al.,[5] attribution could not be determined in this study and therefore conclusions are limited. Further research examining attribution and liver dysfunction related to high-dose paracetamol in opioid-paracetamol combinations is needed.

This study is limited by the use of claims data that do not measure actual use of the medication; however, the intent of the study was to determine prescribing and dispensing practices that put patients at risk. Therefore, claims data is a viable source of information. Also, since pharmacy and medical claims were used, beneficiaries who paid

cash for their medications were not examined. In addition, paracetamol in non-opioid products was not examined. Inclusion of non-opioids would add to the daily dosages received and, therefore, our study provides a conservative examination of paracetamol use. Data from only one health benefit organization were utilized, and results may have been influenced by the characteristics of the organization. Because of the observational study design, a cause-effect relationship between the opioid-paracetamol prescription and liver toxicity cannot be established. In addition, beneficiaries with pre-existing liver disease were not identified and excluded. The regression model showed a small r-squared value, suggesting that our model explains few of the reasons for high-dose prescribing. However, because of the nature of the data used (claims data), only a limited number of variables available in the dataset can be included. Finally, it was assumed that all beneficiaries were healthy patients whose maximum recommended paracetamol daily dose was 4 g/day.

Efforts are being employed by the US FDA to limit excessive use of paracetamol in opioid combinations. Additional approaches may involve the prescriber, pharmacist, benefit manager, health system, regulatory agency and patient. Education of prescribers (especially those professions with higher odds of prescribing the high dose) and dispensers is important in order to alter their thought processes. A requirement that a maximum number of tablets per day be added to the prescription and dispensing label would help ensure dosages are not exceeded.

## Conclusions

Although most opioid-paracetamol prescriptions are for paracetamol daily doses <4 g/day, a large proportion (8.1%) of opioid-paracetamol prescriptions are for an excessive daily dose of paracetamol. This puts over one-quarter of a million (255 123) beneficiaries who are receiving an opioid-paracetamol product at greater risk for toxicity. Multiple factors, including type of opioid- paracetamol product, geographical location, strength of paracetamol in the opioid-paracetamol product and prescriber specialty, were associated with high-dose paracetamol prescriptions. Knowledge of these variables will help to direct future efforts aimed at limiting excessive paracetamol use. Finally, nearly one-quarter of beneficiaries who developed liver dysfunction received a prescription for an opioid-paracetamol product. Efforts to curtail prescribing >4 g/day of paracetamol in opioid combinations may involve provision of prescriber and pharmacist education, changes in prescription and labelling practices, utilization of benefit manager systems to flag excessive dosing and/or require confirmation of dosing, and implementation of FDA recommendations that are supported by these data.

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