# Duration of Use of Hydrocodone/Acetaminophen, Immediate Release Oxycodone, and Extended Release Morphine in a Commercially Insured Population

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## INTRODUCTION

- Hydrocodone/acetaminophen is an immediate-release (IR) opioid indicated for the relief of moderate to moderately severe pain.
- Long-term use of hydrocodone/acetaminophen for the treatment of chronic pain in United States clinical practice has not been extensively described in the literature.
- One study suggests that the incidence of chronicity among individuals prescribed non-liquid formulations of combination hydrocodone products (Ingenix Employer Solutions) was 2.0%, with chronicity defined by both duration of treatment and dose (i.e., at least 20mg/day during a 3-month period).[1]
- Additionally, a drug utilization review conducted by the FDA Office of Surveillance and Epidemiology found that 10% of patients (Source HealthCare Analytics ProMetis Lx®) continued hydrocodone combination products for more than 109 days.[2]

## OBJECTIVES

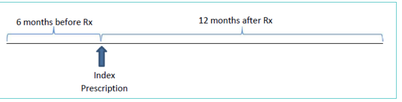
- The objectives of the current study were to assess, among patients newly starting therapy with hydrocodone/acetaminophen (HYD/APAP), the duration of use (i.e., number and proportion of patients with >90 days of continuous therapy), dose of both hydrocodone and APAP, and diagnoses associated with use >90 days.

## METHODS

- **Study design:** retrospective cohort study
- **Dataset:** MarketScan Commercial Insurance database, January 2008-September 2012
- **Inclusion criteria:**
  - Patients 18-64 years of age
  - New* prescription for hydrocodone/APAP
  - New* prescription for a comparator opioid
    - o immediate-release oxycodone (IRO) (consisting of both single-entity and combination products)
    - o extended-release morphine (ERM) prescription
  - 18 months insurance enrollment (6 months before and 1 year after the index prescription (Figure 1).

  * Existing patients (those with prior prescriptions in the 6 month baseline period) were excluded.
- **Study Outcomes:**
  - Daily dose at index prescription
  - Duration of continuous use (no gaps in supply ≥15 days)
  - Number and proportion of patients receiving long-term treatment (continuous use >90 days)
  - Diagnoses at treatment initiation stratified by duration of continuous use
  - Average daily dose by duration of continuous use
  - Number and proportion of patients receiving APAP doses ≥4g
  - Proportion of days at different APAP dose levels
- **Sensitivity analysis:**
  - In January 2011, the FDA requested that, by January 2014, the dose per unit of APAP in APAP products and combinations be limited to no more than 325mg. Affected products may be reformulated at different times.[3]
  - Therefore, a sensitivity analysis was conducted assuming dose of APAP was 300mg/tablet for all tablets containing >325mg APAP. No changes were made to tablets strengths ≤325mg APAP.

### Figure 1. Prescription Index Date and Continuous Enrollment Period




## RESULTS

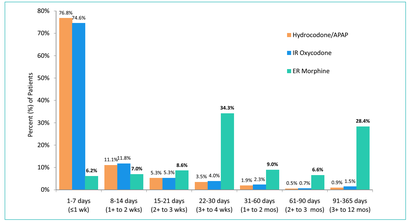
### Table 1. Demographics

| | Hydrocodone/APAP n=4,717,033 | | IR Oxycodone n=1,798,612 | | ER Morphine n=50,615 | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **Age category** | | | | | | |
| **18-24 years** | 514,006 | 10.9% | 172,543 | 9.6% | 1,471 | 2.9% |
| **25-34 years** | 785,698 | 16.7% | 318,636 | 17.7% | 4,834 | 9.6% |
| **35-44 years** | 1,050,947 | 22.3% | 410,617 | 22.8% | 10,053 | 19.9% |
| **45-54 years** | 1,300,107 | 27.6% | 489,243 | 27.2% | 18,247 | 36.1% |
| **55-64 years** | 1,066,275 | 22.6% | 407,573 | 22.7% | 16,010 | 31.6% |
| **Region** | | | | | | |
| **Northeast** | 470,107 | 10.0% | 364,740 | 20.3% | 5,205 | 10.3% |
| **North Central** | 1,216,776 | 25.8% | 352,866 | 19.6% | 11,953 | 23.6% |
| **South** | 2,018,716 | 42.8% | 741,011 | 41.2% | 18,993 | 37.5% |
| **West** | 921,341 | 19.5% | 299,539 | 16.7% | 13,455 | 26.6% |
| **Unknown** | 90,093 | 1.9% | 40,456 | 2.3% | 1,009 | 2.0% |
| **Gender** | | | | | | |
| **Male** | 2,110,199 | 44.7% | 743,680 | 41.4% | 22,963 | 45.4% |
| **Female** | 2,606,834 | 55.3% | 1,054,932 | 58.7% | 27,652 | 54.6% |

### Table 2. Median Dose (mg/day) at Index Prescription

| | Hydrocodone/APAP | | IR Oxycodone | | ER Morphine |
|---|---|---|---|---|---|
| | HYD | APAP | Single-Entity | Combination | |
| **Dose at Index (mg/day)** | 33.3 | 3000 | 50 | 37.5 | 45.0 |

### Figure 2. Duration of Continuous Use, Categorized



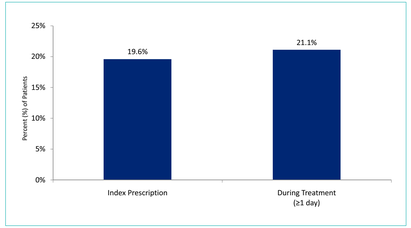

### Table 3. Number of Patients Receiving Long-term Treatment (>90 Days Continuous Use)

| | Number of patients initiating treatment | Number of patients continuing long-term (> 90 days) | Ratio vs. ER morphine |
|---|---|---|---|
| Hydrocodone/APAP | 4,717,033 | 42,386 | 2.95 |
| IR oxycodone | 1,798,612 | 26,840 | 1.87 |
| ER morphine | 50,615 | 14,367 | 1 |

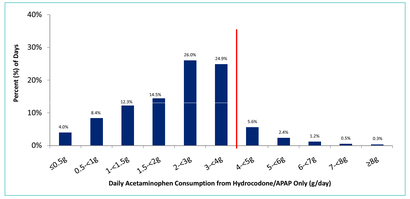
### Table 4. Median Dose (mg/day) During Treatment (Overall and Stratified by Duration of Continuous Use)

| | Hydrocodone/APAP | |
|---|---|---|
| | Hydrocodone | APAP |
| Overall | 33.3 | 3000 |
| By Duration of Continuous Use | | |
| ≤ 3 months | 33.3 | 3000 |
| >3 months | 26.1 | 1651 |

### Figure 3. Proportion of Patients with ≥4g of Acetaminophen Exposure at the Index Prescription and at Any Time During Continuous Hydrocodone/APAP Treatment

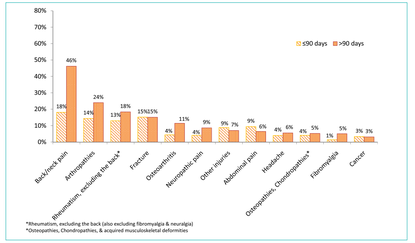



### Figure 4. Distribution of Total Acetaminophen Dose During Continuous Hydrocodone/APAP Treatment (total person-time of exposure = 38,322,339 days)



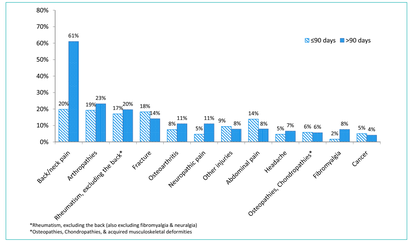

### Figure 5. Pain Conditions at Treatment Initiation by Duration of Continuous Use (≤90 days vs. >90 days)

#### Figure 5A. Hydrocodone/APAP



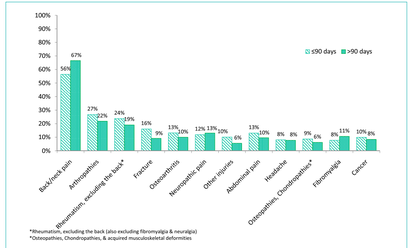

*Rheumatism, excluding the back (also excluding fibromyalgia & neuralgia)
*Osteopathies, Chondropathies, & acquired musculoskeletal deformities

#### Figure 5B. IR Oxycodone




*Rheumatism, excluding the back (also excluding fibromyalgia & neuralgia)
*Osteopathies, Chondropathies, & acquired musculoskeletal deformities

#### Figure 5C. ER Morphine




*Rheumatism, excluding the back (also excluding fibromyalgia & neuralgia)
*Osteopathies, Chondropathies, & acquired musculoskeletal deformities

**Patient Characteristics**

- In the MarketScan Commercial database covering 100 million insured individuals, there were 4.7 million new hydrocodone/APAP users; 1.8 million new IR oxycodone users; and 50,615 new ER morphine users who met enrollment criteria.
- The majority of the three samples were females; younger individuals (18-34 years) comprised a greater proportion of the two IR opioid samples than the ER morphine sample (Table 1).
- The median daily dose of the index prescriptions are shown in Table 2.
  - Most (93.4%) of the IR oxycodone sample used combination products and only 6.6% used single-entity.

**Long-term use**

- Only a small percentage of the hydrocodone/APAP and IR oxycodone users (0.9% and 1.5%, respectively) continued use for >90 days (Figure 2), though the absolute number of patients meeting this criterion was large (hydrocodone/APAP: n=42,386; IR oxycodone: n=26,840) (Table 3).
- In contrast, 28.4% of ER morphine patients (n=14,367) continued use for >90 days (Figure 2; Table 3).

**Dose during Treatment**

- During continuous treatment, the median daily hydrocodone dose was similar for long (>90 days) and shorter (≤90 days) term users. However, dose of APAP was higher among the shorter term users (Table 4).
- At index, 19.6% (n=923,594) of the hydrocodone/APAP patients were prescribed ≥4g APAP; a similar number (21.1%, n=996,306) had at least one day during treatment with prescriptions totalling ≥4g APAP (Figure 3).
  - In the sensitivity analysis, the proportion drops to 5% (both at index and ≥1 day of treatment), however, the absolute number of patients was still substantial (>225,000).
- Figure 4 presents the proportion of days spent on various APAP doses (categorized) during treatment.
  - Approximately 50% of the days were spent on doses between 2g and <4g APAP (>53,000 person-years), and 10% on doses ≥4g (>10,000 person-years).
  - In the sensitivity analysis, the distribution shifted to the left (towards lower APAP doses), though even assuming all APAP doses were 325mg/tablet or below, there would be >1,800 person-years on doses at or above the 4g maximum daily limit set by the FDA.

**Pain Conditions**

- The most common pain conditions diagnosed in the month prior to or following the index prescription are presented in Figure 5 (A-C) – back/neck pain was the most common.

## STRENGTHS AND LIMITATIONS

- Administrative claims databases provide a rich resource, with large sample sizes and detailed prescription refill patterns.
- However, prescription claims data represent prescriptions filled rather than prescriptions taken which could lead to overestimation of utilization.
- Assumptions made about utilization could influence the results:
  - Early refills were assumed to be used only after prior prescriptions had been exhausted.
  - Results for continuous use may vary depending on length of the allowable gap.
- Prescription medication use is not accounted for during periods of hospitalization.
  - Could lead to misclassification of patients as "new" users if they were hospitalized prior to the index prescription.
  - Could lead to underestimation of utilization.
- Each index drug was considered separately, so no information is available about overall duration of continuous opioids or monotherapy vs. multiple pain medications
- Patients were required to have insurance coverage for 18 continuous months, so the sample may not be generalizable to all patients newly dispensed the index opioids.
- The APAP dosing calculations included only acetaminophen from hydrocodone/APAP; patients could also use other prescription or over the counter (OTC) acetaminophen products, further increasing daily acetaminophen dose.
  - OTC medications are not captured within this administrative claims database, so inclusion in the daily acetaminophen dose is not feasible.
  - Acetaminophen is one of the most widely used analgesic compounds worldwide, included in hundreds of products[4], so the impact of these products could be large.
- Due to FDA recommendations, the levels of APAP per dosage unit are expected to be limited to 325mg by January 2014; affected products may be reformulated at different times. Therefore, we conducted a sensitivity analysis to explore how limiting the per unit dosage maximum could change our results.
  - It is important to note that while this sensitivity analysis may provide some insight into possible acetaminophen exposure, it is not known whether the reduction in acetaminophen per unit will affect utilization patterns, which could result in different patterns of both hydrocodone and APAP exposure.

## CONCLUSIONS

- Only a small proportion of patients who initiated hydrocodone/APAP therapy in the database continued treatment for longer than 3 months (0.9%).
- However, the number of patients who continued hydrocodone/APAP for longer than 3 months was over 40,000, 3 times more than the number of ER morphine users and 1.6 times more than that of IR oxycodone users who continued for >3 months.
- The most common pain condition among all three samples was back/neck pain.
- A large number of patients on hydrocodone/APAP were prescribed at least one day of ≥4g acetaminophen at index or during the study.
- In this population of 100 million commercially insured people in the US, hydrocodone/APAP was extensively used to treat chronic pain, 3 times more frequently than ER morphine.

## REFERENCES

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## Conflict of Interest

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