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PRESCRIPTION ACQUIRED ACETAMINOPHEN USE AND POTENTIAL OVER-USE PATTERNS: 2001 - 2008

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Abstract

BACKGROUND—FDA advisory-committees recently made some recommendations to address acetaminophen (APAP)-related toxicity.

OBJECTIVES—To study the proportion of APAP-users potentially consuming APAP over the currently recommended dose (4gm/day) and a toxic dose (10gm/day). To explore the impact of substituting the APAP-strength in combination-prescriptions to 325mg on potential APAP-overuse patterns.

METHODS—Using the 2001-2008 pharmacy claims from IMS LifeLink Health Plans, APAP potential maximum daily dose (PMDD), potential cumulative dose and potential average daily dose (PADD) were calculated annually for APAP-users. The proportion of users with potential APAP-use above 4gm/day and 10gm/day are reported. Analyses were repeated by substituting the maximum APAP-strength in combination-prescriptions to 325mg. Ordinary least squares regression was used to detect linear trends in APAP-use/overuse.

RESULTS—790,188 of 2,656,161 study subjects were prescribed acetaminophen in one or more years from 2001-2008. The proportions of adult APAP-users with PMDD >4gm/day and PADD >4gm/day significantly decreased ($p=0.0020$ and $p=0.0024$ respectively). If the maximum APAP-strength in combination-prescriptions was 325mg, the proportion of APAP-users with PMDD >4gm would be 14.08% in 2001 and 13.67% in 2008 while the proportion of those with PMDD >10gm would be 0.21% and 2.30%.

CONCLUSION—About 1 in 4 APAP-users have a PMDD >4gm/day while 2-3% have a PMDD >10gm based exclusively on prescription data which is concerning. These proportions could reduce by over half if the maximum APAP-strength in combination-prescriptions is 325mg. Additional monitoring of opioid prescription-patterns, physician and pharmacist cognizance in prescribing APAP-containing combination products and dose reduction strategies should be considered to reduce APAP-overuse.

INTRODUCTION

FDA advisory committees recently made a number of recommendations to address the toxicity of acetaminophen (APAP), a commonly used analgesic-antipyretic.¹ In the US, acetaminophen over-dose accounts for approximately 56,000 emergency room visits, 26,000 hospitalizations and 458 deaths annually.² Though doses above 10gms/day are associated with hepatotoxicity in adults³, cases of hepatotoxicity have also been reported near the recommended maximum doses (4gms/day).^{4,5} The proportion of acetaminophen-induced

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acute liver failure cases increased from 28% in 1998 to 51% in 2003.⁶ In January 2011, the FDA mandated that the manufacturers of APAP-containing combination-prescriptions limit the APAP-strength in these products to 325mg.⁷

Although chronic APAP-use has been linked hepatotoxicity in case reports⁵, large-scale studies establishing this association are lacking. Studies regarding acetaminophen over-use lack data on acute and chronic APAP-use patterns in commercially insured populations.⁸⁻¹⁰ Using a commercial insurance claims database, we studied the proportion of adult acetaminophen users (≥ 12 years of age) who potentially consumed more than the recommended APAP dose (4gms/day) or a toxic dose of 10gms/day. We also studied the proportion of children (< 12 years of age) who potentially used more than the recommended pediatric APAP dose (75mg/kg). Furthermore, we explored the impact of substituting the maximum APAP-strength in combination-prescriptions to 325mg on potential APAP-overuse patterns.

METHODS

This was a retrospective cross-sectional study of a 10% random sample of the IMS LifeLink Health Plans data from 2001 to 2008. The data is representative of the commercially insured population in the US with respect to age, gender and region.

This study included enrollees continuously eligible for pharmacy benefits for 12 months during any calendar year from 2001-2008. 'Acetaminophen-users' were defined as those with at least one prescription for an acetaminophen-containing product based on the Generic Product Identifier (GPI) codes. Based on potential maximum daily dose (PMDD) and potential average daily dose (PADD) calculations adult users were classified as those with a potential use above and below/at the currently recommended dose (4gms/day) and a toxic dose of 10gms/day.

Pediatric users were classified as those with PMDD above and below/at the recommended dose of 75 mg/kg.¹¹ Due to unavailability of patient weight in the data, U.S. average gender-age based weights from the National Health Statistics Report¹² were used to determine the age and gender overuse thresholds. We repeated the analyses by substituting the maximum APAP-strength in combination-prescriptions to 325mg.

Acetaminophen utilization measures

Potential maximum daily dose (PMDD): The highest potential APAP-dose on each day during a calendar year was calculated using the days-supplied, strength, and quantity fields in the data. Overlapping prescriptions were identified using fill dates and days-supplied and the daily doses were summed to obtain the potential maximum dose. We calculated the total days of potential overuse (sum of consecutive and non-consecutive days), maximum uninterrupted duration of potential overuse and number of scripts in each potential overuse interval.

Potential average daily dose (PADD): Dose obtained by summing up the APAP doses contained in all prescriptions and dividing by the total days-supply.

Potential annual cumulative dosage: The sum of acetaminophen dose (quantity*APAP-strength) from all acetaminophen-containing prescriptions during a calendar year.

ANALYSIS

Trends in potential APAP-use/overuse were tested using crude ordinary least squares regression models with linear-trend terms. This study was approved by the Institutional Review Board of the University of Arkansas for Medical Sciences.

RESULTS

Of the 2,656,161 unique eligible subjects across 2001-2008, 47.23% were women and the mean age was 30.41 years. 29.75% of these (790,188 individuals) used acetaminophen in one or more years. The annual proportion of APAP-users remained relatively constant; 15.90 % in 2001, and 17.76% in 2008 ($p=0.0697$).

Among the adult APAP-users from 2001 to 2008, the percentages of those with PMDD >4gm/day and those with PADD>4gm/day decreased significantly ($p=0.0020$ and $p=0.0024$ respectively) while there was no significant trend in the proportions of those with potential maximum or average daily doses >10gm/day (**Table 1**). If the maximum APAP-strength in combination-prescriptions was 325mg, the proportion of those with PMDD >4gms/day would be 14.08% and 13.67% in 2001 and 2008 respectively and the proportion of those with PMDD >10gms/day would be 0.21% and 2.30%. The average 'total duration' (interrupted and uninterrupted) of potential APAP-use > 4gms/day was 10.65 days across 49,836 PMDD-based APAP over-users in 2008. 24.44% of these users had a 'total duration' of potential over-use of more than 7 days. Among users with PMDD >4gm/day and those with PMDD >10gm/day, the proportions of individuals with more than 7 days of maximum consecutive potential overuse duration significantly increased from 2001-2008 ($p = 0.0085$ and $p=0.0020$ respectively) (**Table 1**). Among 6,820 users with potential maximum consecutive over-use >7 days in 2008, 40.58% were prescribed a single APAP-containing script while among 43,016 individuals with < 7 days of consecutive over-use, 24.92% used a single script.

The mean potential annual cumulative acetaminophen dose for adult users increased from 55.29gms (95% CI: 54.22, 56.35) in 2001 to 81.94gms (95% CI: 80.56, 83.32) in 2008 ($p=0.0039$). Only 0.38% of the adult patients in 2008 potentially used more than equivalent of 4gms/day over an entire year. Narcotic-APAP combinations accounted for over 90% of all APAP-containing prescriptions among adults and about 50% of APAP-containing prescriptions among children.

4.03% and 5.71% of the pediatric subjects consumed acetaminophen in 2001 and 2008 of which 12.90% and 13.95% had a PMDD above the recommended age-weight based dose. Among children below 18 years of age in 2008, the proportion likely to exceed the recommended dose was the highest in the 15-17 year old group (18.94%) followed by those 0-2 years (18.89%) with the smallest proportion in the 9-11 year olds (9.22%) (**Figure 1**).

DISCUSSION

It is concerning that over a quarter of the APAP-users have a potential peak APAP-consumption over 4gms/day based exclusively on prescription claims. Of particular alarm is the finding that nearly 3% of the APAP-users had a PMDD >10gms/day, a dose linked to hepatotoxicity.³ The proportion of all enrollees with a PMDD >4gms varied between 5.99% and 5.38% and is similar to the proportions reported for California⁹ (5.9%) and Oregon Medicaid⁸ (4.0%). These data suggest that APAP-overuse is not only a concern in vulnerable Medicaid populations, but it may also be an equal or greater concern in the commercially insured populations. Although smaller than the proportions based on PMDD, the proportions of potential over-users based on PADD are still concerning.

Approximately three in four APAP users with a PMDD >4gms for 1-3 consecutive days potentially used a single APAP-containing script and likely did so as a 'take as needed' pro-nata (PRN) prescription. An example from the dataset is a prescription for 40 tablets of Lortab (5mg Hydrocodone, 500mg APAP) with a 3-day supply. Assuming that a maximum of 12 tablets could be taken daily (2 tablets /4 hours in 24 hours), a pharmacist would likely enter a three or four day supply. Actual use of an acute PRN analgesic may be less than the calculated PMDD based on 'days-supply' and 'quantity' fields for a significant proportion of these patients. Nevertheless, physician and pharmacist cognizance of the maximum daily APAP dose should guide the instructions and counseling of those prescribed opioid/APAP combination products. In addition, such counseling should include clear and concise instructions on the maximum number of dosages (tablets, capsules, mls) that can be safely consumed within a 24 hour period. About a quarter of the APAP-users potentially exceeding the 4gms threshold for 1-3 days possibly used multiple overlapping prescriptions and these brief overlaps might represent 'early-refills', not actual overuse. Nonetheless, nearly half of the recipients had consecutive use potentially exceeding 4 days and nearly a quarter had consecutive use more than a week. These use patterns and the increasing trend in the proportion of APAP users with a PMDD > 4gm and >10gms/day for >7 consecutive days are more likely to represent actual use exceeding the limits and are cause for concern.

Excess acetaminophen use in adults may likely be caused by an increase in acetaminophen-narcotic combination-prescriptions for chronic non-cancer pain.¹³ If the maximum APAP-strength in combination-prescriptions was reduced to 325mg as per a recent FDA mandate, the PMDD-based proportion of APAP-users potentially exceeding the 4gms and 10gms threshold would drop by more than half thus lending support to the rationale behind implementing this policy. The proportion of pediatric recipients potentially exceeding the recommended dose was highest among the adolescents (15-17 years) followed by infants (0-2 years). Among children, confusion over APAP-strength in different products leads to overdose and regulatory changes to pediatric acetaminophen products may overcome this problem. Drug manufacturers now plan to standardize the APAP strength in pediatric liquid products to 160mg/5ml to avoid confusion¹⁴ and since infants have a high rate of excess acetaminophen use, this strategy of streamlining doses appears warranted.

Our results should be interpreted in light of the following limitations. Since OTC-use not billed as a prescription was not recorded in our data, this study reflects only a minimum risk of acetaminophen overuse for some subjects. The acetaminophen product market consists of 48% prescription and 52% OTC products¹⁵ and nearly 80% of acetaminophen doses may be OTC¹⁶, so we may observe only about 20-50% of all acetaminophen use with these data. Conversely, our PMDD calculation relies on 'days-supplied' and 'fill-dates' therefore the assumption of concurrent use of overlapping prescriptions may overstate actual use in certain cases, particularly among nearly 15% of the potential APAP over-users using multiple prescriptions with an overlap period of just 1-3 days (possibility of early refills) and in about 43% of the users potentially exceeding the 4gms threshold for 1-3 days from a single medication, which may often reflect 'PRN' usage. Finally the classification thresholds for children are based on average weights and this might have led to misclassification of some patients.

Based exclusively on prescription claims nearly 1 in every 4 acetaminophen recipients had a PMDD exceeding 4gms while approximately 3% had a PMDD > 10gms/day. PADD-based proportions, although smaller, show that if APAP is indeed used as prescribed, a small proportion of individuals may still have potential consumption above the recommended/toxic dose. Additional monitoring of opioid prescription-patterns, physician and pharmacist awareness in prescribing, acetaminophen-dose reduction strategies and regulatory changes

in pediatric acetaminophen products should be considered to reduce potential acetaminophen overuse.

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Key messages

- Between 2001 and 2008, the proportion of acetaminophen users in the population remained relatively stable.
- About 1 in 4 adult acetaminophen users had a potential maximum daily dose over 4 gm/day while about 3% of the users potentially consumed more than 10gms/day of acetaminophen.
- About 12% of the acetaminophen users had a potential average daily dose of over 4gm/day while about 2% of the users had a potential average daily dose more than 10gm/day. Though less than the proportions based potential maximum daily doses, these percentages are a cause of concern.
- Among pediatric recipients, adolescent users had the highest rate of potential acetaminophen overuse followed by infants.
- Opioid combinations with acetaminophen accounted for over 90% of acetaminophen prescription use among adults. If the maximum acetaminophen strength in combination products is limited to 325mg according to a recent FDA policy, the proportion of potential over-users would be cut by more than half.

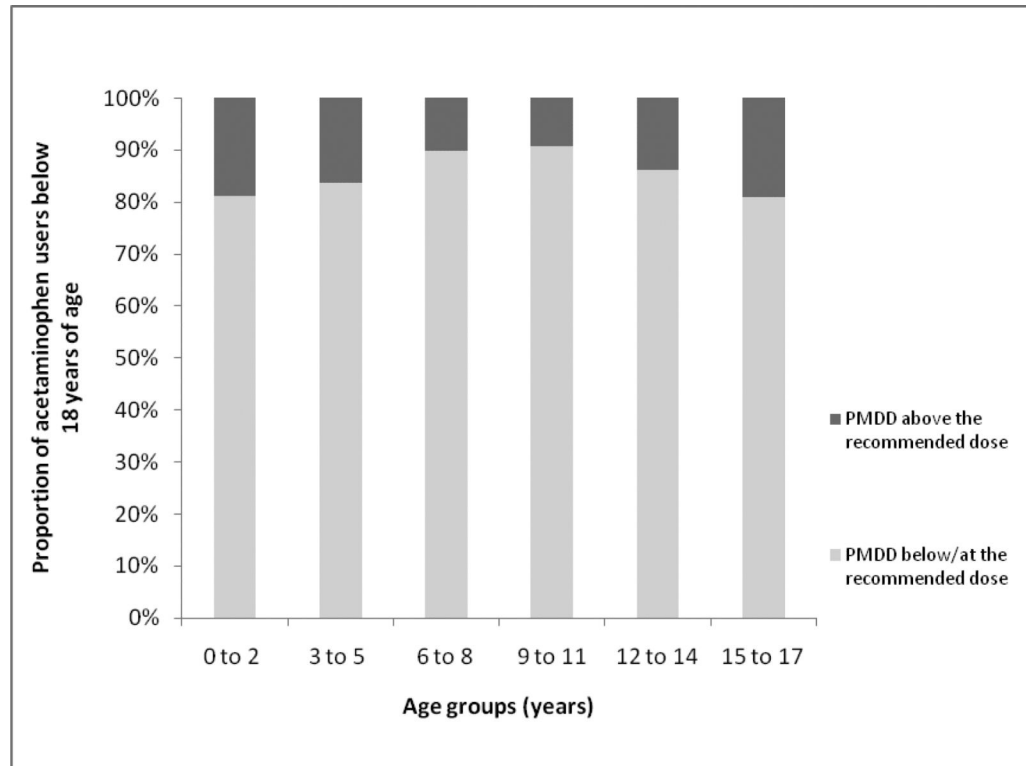


Figure 1. Annual proportion of acetaminophen users < 18 years of age with potential maximum daily dose above and below/at the recommended dose in the year 2008

Table 1

Potential acetaminophen overuse among adult users: 2001-2008

Year	Proportion of APAP users with PMDD >4 gm	Proportion of APAP users PMDD >10 gm	Proportion of APAP overusers (PMDD >4gm) with uninterrupted duration of potential overuse >7 days	Proportion of APAP overusers (PMDD >10gm) with uninterrupted duration of potential overuse > 7 days	Proportion of APAP users with PADD >4 gm	Proportion of APAP users with PADD >10 gm
2001	32.61%	1.88%	11.07%	3.26%	17.67%	0.33%
2002	32.90%	2.11%	10.60%	3.57%	18.12%	0.31%
2003	34.02%	3.56%	10.98%	5.80%	18.73%	0.87%
2004	30.06%	3.01%	11.54%	5.44%	15.23%	0.96%
2005	27.85%	2.08%	11.40%	6.40%	13.63%	0.70%
2006	27.18%	1.51%	11.58%	9.42%	12.82%	0.40%
2007	25.62%	1.22%	12.09%	12.58%	11.51%	0.27%
2008	26.84%	3.17%	13.68%	19.57%	12.93%	2.24%

APAP - Acetaminophen

PMDD – Potential Maximum Daily Dose

PADD – Potential Average Daily Dose

* denominator is the number of adult APAP users

** denominator is the number of APAP users with a PMDD > 4gm/day

*** denominator is the number of APAP users with a PMDD > 10gm/day