Variability in Acetaminophen Labeling Practices: a Missed Opportunity to Enhance Patient Safety

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Abstract Confusion regarding a drug's active ingredient may lead to simultaneous use of multiple acetaminophen-containing prescriptions and increase the risk of unintentional overdose. The objective of this study was to examine prescription labeling practices for commonly prescribed acetaminophen-containing analgesics, specifically focusing on how active ingredient information and concomitant use warnings were conveyed. Pa-

tients with new acetaminophen-containing prescriptions were recruited upon discharge from an emergency department in Chicago or at an outpatient, hospital-based pharmacy in Atlanta. Label information was transcribed from prescription bottles and patients' knowledge of active ingredient was assessed by in-person interviews. Among the 245 acetaminophen-containing prescriptions, hydrocodone was the most common second active ingredient ($n=208$, 84.8 %) followed by oxycodone ($n=28$, 11.4 %). Acetaminophen was identified by its full name on 6.9 % ($n=17$) of labels; various abbreviations were used in 93.1 % of cases. One hundred forty-seven bottles used auxiliary warning labels with the majority of labels ($n=130$, 88.4 %) warning about maximum dose and 11.5 % ($n=17$) about concomitant use. Most of the study participants ($n=177$, 72.2 %) were not able to identify acetaminophen as an active ingredient in their prescription. There was no significant association between the use of unabbreviated labels including warning information and patients' awareness of acetaminophen as an active ingredient (36.4 vs. 27.3 %, $p=0.50$). We noted high variability in labeling practices and warning information conveyed to patients receiving acetaminophen-containing prescriptions. Missed opportunities to adequately convey risk information may contribute to the burden of acetaminophen-related liver injury.

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Introduction

Acetaminophen overdose has surpassed viral hepatitis as the leading cause of acute liver failure in the USA [1–3]. From 2000–2007, the American Association of Poison Control Centers reported a 70 % increase in cases of unintentional acetaminophen overdose, not including cases with suicidal intent

[4]. Acetaminophen overdose results in at least 30,000 hospitalizations and 50,000 emergency department visits annually [5, 6]. A significant root cause of unintentional acetaminophen overdose and toxicity may be inadequate knowledge of the active ingredient information, leading individuals to take multiple prescription and over-the-counter acetaminophen-containing products together and exceeding the maximum safe dose [7, 8].

Previous investigations, including research by our team, have shown that patients may misinterpret drug labels and cannot recognize acetaminophen as an active ingredient [9, 10], which may facilitate unintentional overdoses. The objective of this manuscript is to describe the prescription labeling practices for common acetaminophen-containing analgesics, specifically focusing on how active ingredient information and concomitant use warnings were conveyed. We also explored whether patients' awareness of acetaminophen as an active ingredient was associated with labeling practices.

Materials and Methods

Between April and October 2011, a total of 552 patients who received a new prescription for an acetaminophen-containing analgesic were consecutively recruited from the emergency department at a large teaching hospital in Chicago or at a hospital-based, outpatient pharmacy in Atlanta. Medical staff in the emergency department in Chicago identified patients prescribed acetaminophen-containing medications to research assistants for recruitment, whereas research assistants in the Atlanta outpatient pharmacy approached patients waiting to fill a medication order and asked to view the prescription to see if they were eligible to be part of the study. In Chicago, patients were able to fill their prescriptions at any community pharmacy of their choice. In Atlanta, all prescriptions were filled at the pharmacy site. Patients were recruited as part of a larger study assessing multiple factors, including patients' recall of counseling and analgesic medication taking behaviors (results reported separately).

Patients were eligible if they were 18–80 years old, English-speaking, and received an acetaminophen-containing prescription. Eligible patients were asked to return for a follow-up study visit within 4–7 days of enrollment and were provided compensation for their time and travel at the return visit. Participants were asked to bring all of their medication bottles to the follow-up interview. At the return visit, research assistants transcribed the label information verbatim, in the order in which it appeared, including ingredient name, abbreviation, dose, frequency, and any warnings pertaining to acetaminophen. All research assistants were oriented to common prescription labels beforehand and were familiar with primary and auxiliary acetaminophen labeling practices that may have been encountered in the study. To assess awareness of

acetaminophen as an active ingredient, participants were also asked to name the pain-relieving ingredients in their prescription. In addition to collecting basic demographic information (age, gender, income, employment status, education level, race, and self-reported current health status), health literacy was assessed at this visit using the Rapid Estimate of Adult Literacy in Medicine (REALM) [11].

Descriptive statistics were used to describe the sample and labeling on prescription bottles: Fisher's exact test was used to assess the association between bottle labeling and patient awareness of acetaminophen in the prescription. All analyses were conducted using STATA software version 12.1 (StataCorp, College Station, TX). Northwestern University and Emory University institutional review boards approved the study.

Results

A total of 435 individuals initially agreed to participate; 22 were screened as ineligible, 249 participants completed return visits, and 245 had their medication bottles available for review. The calculated response rate was 46.4 % using definitions set forth by the American Association for Public Opinion Research [12]. Among the 245 patients with available prescription bottles, the mean age of the study sample was 43 years (SD=11.8). Of the participants, 53.5 % were female, 66.9 % were African American, and 22.9 % were Caucasian. On average, half of patients had limited health literacy, 59.2 % had a yearly income less than \$20,000, and 60.0 % were unemployed (Table 1).

Among the 245 acetaminophen-containing prescriptions, hydrocodone was the most common second active ingredient ($n=208$, 84.8 %) followed by oxycodone ($n=28$, 11.4 %). Only three bottles included a brand name on the label; the rest appeared to be generic.

Seventy-five percent of patients received prescriptions with 5 mg of hydrocodone; 20 % received prescriptions containing 10 mg of hydrocodone. The remaining 5 % consisted of the other combination medications. The acetaminophen dosage was distributed nearly evenly between the 325- and 500-mg strengths (53 and 46 %, respectively). Information about duration was rarely included: only nine prescriptions had duration noted by the provider in the sig line of the prescription. Data on the number of refills is not available.

Acetaminophen labeling and use of "concomitant use" warnings are presented in Table 2. Acetaminophen was identified, on the primary label, by its full name on 6.9 % ($n=17$) of prescription labels; abbreviations were used in 93.1 % of cases. The most commonly used abbreviations were "ACET" ($n=125$, 54.8 %) and "APAP" ($n=90$, 39.5 %). A total of 5.2 % ($n=12$) prescription bottles had other abbreviations such as "ACETAM," "ACETAMIN," and "ACETAMINOPH."

Table 1 Baseline demographics and characteristics of study sample

Variable	All participants (N=245)
Age, mean (SD)	43 (11.8)
Female, %	53.5
Race, %	
African American	66.9
White	22.9
Other	10.2
Health literacy, %	
Adequate	58.4
Limited	41.6
Education, %	
High school or less	47.8
Some college	27.3
≥College graduate	24.9
Income, %	
<\$20,000	59.2
\$20,000–\$50,000	20.6
>\$50,000	20.2
Unemployed, %	60.0
Recruitment site	
Emergency department (Chicago), %	44.1
Hospital pharmacy (Atlanta), %	55.9

Auxiliary warnings placed by pharmacists were present on 60.0 % ($n=147$) of bottles. Among the warning labels, the majority ($n=130$; 88.4 %) were maximum dose warnings, whereas 11.5 % ($n=17$) were concomitant use warnings (specifically advised not to take other acetaminophen-containing products). Concomitant use warnings were present on 6.9 % of all prescription labels. And no warnings against use in combination with alcohol were noted. Slightly more than half (55.7 %) of labels contained both an abbreviation for acetaminophen along with an auxiliary warning label; 4.5 % ($n=11$) of prescriptions included the full name of the drug as well as a warning label.

In exploratory analyses examining patients' awareness of active ingredients, most study participants ($n=177$, 72.2 %) were not able to identify acetaminophen as a pain-relieving ingredient in their prescription. Neither spelling out the full

name (29.4 vs. 27.3 %, $p=0.85$) nor including an auxiliary warning label to identify the active ingredient (29.3 vs. 25.5 %, $p=0.52$) were associated with patients' correct identification of acetaminophen as a pain-relieving ingredient in their prescription. Although patients receiving prescriptions with both the full medication name spelled out and with warning labels had numerically higher rates of identifying acetaminophen as an active ingredient when compared to patients with either an abbreviation for acetaminophen or no warning labels, this difference was not statistically significant (36.4 vs. 27.3 %, $p=0.50$).

Discussion

Overall, we found significant variability in labeling practices for active ingredient and warnings among a large sample of acetaminophen-containing prescriptions. Acetaminophen was identified on the primary container label by its full name on only one in 14 prescriptions. Instead, pharmacies opted to use multiple, ambiguous abbreviations. Less than a third of patients were aware that their prescription medication contained acetaminophen. Although this level of knowledge is low, it is consistent with previously published data wherein only 31 % of patients were able to identify acetaminophen as the active ingredient in Tylenol® [9]. Some of the commercial manufacturers of acetaminophen products are currently attempting to address this lack of knowledge through changes in labeling; since 2013, "Contains acetaminophen. Always read the label" has been imprinted on the caps of brand name, over-the-counter acetaminophen bottles. However, this change in labeling of the over-the-counter products only addresses one of the possible avenues towards overdose and does not solve the problem described above with inconsistent labeling of *prescription* acetaminophen products. The National Council for Prescription Drug Programs (NCPDP) recently made a recommendation for the complete spelling of acetaminophen in all prescription products; the impact of this recommendation has not yet been evaluated [13].

Another concerning finding in our data was the lack of concomitant use warnings (present on 6.9 % of prescription bottles). Even if active ingredients are clearly indicated on

Table 2 Contents of acetaminophen-containing prescription labels (N=245)

Label information (N=245)	Total, n (%)	Maximum dose warning	Concomitant use warning	No warning
Acetaminophen	17 (6.9)	11 (64.7)	0 (0.0)	6 (35.3)
"ACET"	125 (51.0)	56 (44.8)	14 (11.2)	55 (44.0)
"APAP"	90 (37.7)	52 (57.8)	3 (3.2)	35 (38.9)
Other abbreviation	12 (4.9)	11 (91.7)	0 (0.0)	1 (8.3)
Acetaminophen not labeled	1 (0.4)	0 (0.0)	0 (0.0)	1 (100.0)

prescriptions, patients may not recognize it as the same medication due to thinking of over-the-counter medications by brand name (e.g., Tylenol® or TheraFlu®). Specific warnings drawing attention to both concomitant use and the risk for overdosing or liver damage may therefore be useful. The effect size of such labeling changes is difficult to estimate. Regardless of the impact, it seems clear that variability in pharmacy labeling is a missed opportunity to promote medication safety. These variable practices may lead to patient misinformation and adverse clinical consequences. Patient-centered warning and ingredient labels have been proposed as a solution; to have the greatest impact labels would need to be consistent across both over-the-counter and prescription products.

There are several limitations to this study we must acknowledge. We assessed practices from one hospital-based pharmacy and a limited number of other pharmacies serving patients seeking care at only two large urban centers. The lack of awareness of the acetaminophen component of the medication was high in this study and very few patients received a label with acetaminophen completely spelled out, which affected our ability to adequately assess the impact of this labeling practice on awareness of the active ingredient. The study was also not designed to examine the effect of labeling practices or auxiliary warnings on clinical outcomes such as acetaminophen toxicity or overdose. The overall cooperation rate was 46 %; however, we feel that this is acceptable given that patients were prescribed medications for painful conditions possibly precluding return study visits.

The lack of standardized labeling practices for acetaminophen is a missed opportunity to promote medication safety that can be remediated. The American Association for the Study of Liver Diseases has recommended the use of more explicit labeling, specific concomitant use and alcohol warnings as well as product package redesign to improve acetaminophen safety [14]. Enforcement of prescription labeling standards in the USA is the responsibility of the Food and Drug Administration (FDA) and State Boards of Pharmacy. Standards or recommendations from organizations like United States Pharmacopeial Convention (USP) are often not implemented until State Boards and/or the FDA adopt them into their regulations. Recent voluntary guidance by the FDA may provide assurances that acetaminophen be spelled out on primary labels, but our research shows this might not be sufficient as a stand-alone strategy to prevent harm to patients [10]. This study demonstrates the importance of the FDA and State Boards of Pharmacy to set a single, clear standard for labeling acetaminophen as an active ingredient and require uniform warnings about concomitant use of acetaminophen-containing products.

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