ORIGINAL RESEARCH

Risk of Unintentional Overdose with Non-Prescription Acetaminophen Products

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BACKGROUND: There is increasing concern over the risk of consumer unintentional misuse of non-prescription (a.k.a. 'over-the-counter') medications containing acetaminophen, which could lead to acute liver failure.
OBJECTIVE: To determine the prevalence of potential misuse and overdose of over-the-counter medications containing acetaminophen, either alone or in combination.
DESIGN: Cross-sectional, structured interviews with literacy assessment.
SETTING: One academic and one community-based general internal medicine practice in Chicago, IL, and one academic general internal medicine practice and a public hospital clinic in Atlanta, GA.
PATIENTS: Five hundred adults seeking primary care, ages 18–80.
MEASUREMENT: Demonstration of how and when patients would take over-the-counter medications containing acetaminophen, alone or in combination with one another, over a 24-hour period.
RESULTS: Overall, 23.8 % of participants demonstrated they would overdose on a single over-the-counter acetaminophen product by exceeding a dose of four grams in a 24-hour period; 5.2 % made serious errors by dosing out more than six grams. In addition, 45.6 % of adults demonstrated they would overdose by 'double-dipping' with two acetaminophen-containing products. In multivariable analyses, limited literacy (Relative Risk Ratio (RR) 1.65, 95 % Confidence Interval (CI) 1.03–2.66) and heavy acetaminophen use in the past six months (RR 1.70, 95 % CI 1.10–2.64) were independently associated with overdosing over-the-counter products.
CONCLUSION: Misunderstanding of the active ingredient and proper instructions for over-the-counter medications containing acetaminophen is common. The potential for errors and adverse events associated with unintentional misuse of these products is substantial, particularly among heavy users of acetaminophen and those with limited literacy.

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One of the most common health behaviors among adults is the occasional or even everyday use of non-prescription, or 'over-the-counter' (OTC) medication products for a wide range of indications. Almost half (42 %) of U.S. adults take at least one OTC medication on a regular basis.[1] The ease of access to OTC drugs, however, presents a challenge to patient safety; many individuals may lack the requisite health literacy skills to appropriately self-administer these medicines. Unlike prescription drugs that require a learned intermediary (i.e. physician) to gain access and provide instruction for the safe use of a medication, individuals make independent decisions that match an OTC product to a self-diagnosed symptom or condition. Product labeling, while standardized by the Food and Drug Administration (FDA) since 1999, becomes the primary and often only means for one to learn about a medication.[2] This includes knowledge of the active ingredient, indication(s), directions for use, and side effect profile. A few studies suggest many adults misinterpret OTC product instructions or not carefully heed them.[3–6]

Recent attention has been focused on the unintentional misuse of OTC pain medication, and acetaminophen specifically, which is the most commonly-used OTC product in the U.S. with 19 % of adults reporting taking the drug in a given week.[7–10] Acetaminophen overdose is the leading cause of acute liver failure.[11–13] In 2009, the FDA convened a panel to review the existing evidence and characterize the problem of acetaminophen overdose. The panel concluded that 1) limited evidence is available, 2) the majority of overdoses appear unintentional, and 3) OTC drug labeling is a likely root cause.[14] Since then, a qualitative study by King and colleagues eluded to widespread consumer confusion and ambivalence towards knowing the various active ingredients in OTC pain

products like acetaminophen, and a failure to adequately recognize the risks associated with misusing these medicines.[3]

We sought to determine the prevalence of misunderstanding and potential misuse of OTC products containing acetaminophen. Misuse was defined as either 1) incorrectly dosing out a single acetaminophen-containing product, 2) exceeding the recommended maximum daily dose, or 3) identifying that it would be safe to take two acetaminophen-containing OTC drugs in combination (a.k.a. 'double-dipping'). Findings from our study fill existing gaps in the literature, identified by the 2009 FDA panel, on the extent and nature of the problem of acetaminophen misuse, and offer evidence to guide future public health and health system responses.

METHODS

We conducted a cross-sectional study consisting of structured, in-person interviews among adult patients receiving care at outpatient general medicine clinics in Atlanta, GA and Chicago, IL.

Sample

English-speaking adults waiting for an appointment with their physician at one of four clinics (2 per city) were recruited to the study beginning September 2009 through March 2011. At each location, one of the sites was an academic-affiliated general internal medicine clinic, while the other was a community health center. Patients were deemed eligible to participate if they were ages 18 to 80, and without a hearing, visual, or cognitive impairment (as determined by direct communication with the patient, Snellen eye chart, and the six-item screener cognitive assessment[15]). Patients were randomly selected to be recruited to the study based on a clinic seating chart. If this was not possible due to low volume, a consecutive sampling scheme (every other patient) was employed. Participants were compensated $10 for their time. A total of 500 patients consented and participated in the study, equally recruited between the two locations (n=250 per city) and across clinics (n=125 per clinic). Overall, 1013 patients were approached among the four clinics, 307 declined participation, 114 were found to be ineligible, and 92 subjects did not fully complete the interview. Based on American Association for Public Opinion Research (AAPOR) guidelines, our final participation rate was 56 %.[16] Institutional Review Boards at Northwestern University, Emory University, Mercy Hospital (Chicago) & Grady Memorial Hospital (Atlanta) approved this study.

Measurement & Procedure

We tested patients' functional understanding and demonstrated use of OTC acetaminophen products via 1) *proper dosing* of a single OTC medication over a 24-hour period, and 2) risk of '*double-dipping*' or the perceived safety of simultaneously taking two acetaminophen-containing products. To assess proper dosing, subjects were given five OTC drug bottles (Tylenol® Rapid Release Extra Strength Gels [500 mg acetaminophen/gelcap], Advil® Liqui-Gels [200 mg ibuprofen/capsule], Aleve® Liquid Gels [200 mg naproxen sodium/capsule], CVS® Brand Arthritis Pain Relief [650 mg acetaminophen/caplet, and Excedrin® Extra Strength [250 mg acetaminophen/tablet]), one at a time for review. For each medicine, the interviewer would ask, "Imagine that you took your first dose at [time]. You want to take the maximum dose of this medicine for one day. Starting with your first dose at [time], show me how many pills and at which times you would take them for a full 24-hour day." A 4 x 6 dosing tray with 24 compartments, each identifying an hour of day, was placed in front of the subject for them to place pills at the times at which they would take them. The order in which the five medicines were presented for the dosing exercise was randomized to account for any learning effect. Interviewers also recorded whether participants paid attention to the instructions on the bottle.

To assess double-dipping, patients were presented with three scenarios in which the subject was told to imagine they were taking a maximum dose of a primary OTC drug (Tylenol® Rapid Release, Advil® Liqui-Gels, Tylenol® Sinus Congestion and Pain [325 mg acetaminophen/caplet]). They were then asked if it would be safe to also take a second medicine with the primary medicine. For each of the three scenarios, three to six secondary non-prescription products were shown to the participant individually. Prior experience with the various OTC products used in the different scenarios was assessed through a series of questions, including whether participants had ever taken the specific brand name or generic products during the last 6 months, and if they ever take more than the indicated amount on the label. Patients' literacy skills were measured using the Rapid Estimate of Adult Literacy in Medicine (REALM), one of the most widely used assessments in health literacy research.[17]

Analysis Plan

Descriptive statistics (percentage, mean and standard deviation) were calculated for each variable. Chi-square and Student's t-tests were used to evaluate associations between patient characteristics and the outcomes of overdosing (yes/no) or double-dipping (yes/no) acetaminophen. Generalized linear models with a Poisson distribution and log link function were used to estimate risk ratios for included covariates compared to each referent condition.[18,19] A Generalized Estimating Equation (GEE) approach was used to adjust model coefficients and standard errors for within-patient correlation as tasks were repeated

using multiple medications.[20,21] Both models for overdosing and double-dipping included the potential confounding variables and risk factors of age, gender, race (black, white, other), literacy (limited (< 9th grade or low + marginal) vs. adequate (≥ 9th grade)), household income, acetaminophen use (non, moderate, heavy), and clinic type (academic vs. community). Since education is strongly associated with literacy, it was examined separately to avoid over-adjustment in final models. This issue has previously been reviewed by Wolf and colleagues.[22] Interaction terms between covariates were included in models to determine whether associations varied according to these characteristics. All statistical analyses were performed using STATA software version 10.0 (StataCorp, College Station, TX).

RESULTS

The sample is described in Table 1. The mean age of participants was 49.3 years (SD=14.8, range 18 to 80 years). Two thirds of participants (62.6 %) were female, and over half were African American (56.8 %). More than a third (38.7 %) had limited literacy skills, as recognized as reading at less than a 9th grade level according to the REALM. Participants were socioeconomically diverse by education and household income. The majority (56.2 %) of patients self-reported some acetaminophen use, with 18.6 % being classified as 'heavy' users (taking it every day or at least a couple days a week during past six months).

Proper dosing of three OTC acetaminophen products was first evaluated, and error rates (overall and by error type) are presented in Table 2. In all, 23.8 % of participants demonstrated they would overdose on one or more OTC acetaminophen products by exceeding a dose of four grams in a 24-hour period; 5.2 % demonstrated serious errors by dosing out more than six grams. Rates of overdosing were highest for the 1000 mg/dose product (17.5 %). The most common error for the 500 mg/dose (2 pills every 6 hours) and 1300 mg/dose (2 pills every 8 hours) products was not waiting long enough between doses (23.5 % and 38.3 % respectively). For the 1000 mg/dose (2 pills every 4–6 hours) product, the most common error was taking too many doses in a 24-hour period (21.8 %).

Scenarios were then presented to participants that assessed their likelihood of taking two acetaminophen-containing products in combination, or 'double-dipping' (Table 3). Nearly half (45.6 %) of subjects demonstrated they would overdose by double-dipping in one or more scenarios including taking two OTC medications containing acetaminophen. When given the brand name base product that contained 1000 mg/dose of acetaminophen only, patients were most likely to state they believed they could take the maximum dose of the base product and also a PM pain reliever containing 1000 mg/dose acetaminophen (21.7 %, $p<0.001$), or a cold and cough medication containing 650 mg/dose of acetaminophen (20.1 %). When the base product was changed to a combination sinus medication containing 650 mg/dose of acetaminophen and patients were again asked if they could safely use these additional medicines beyond the maximum dose of the base products, double-dipping was also most prevalent with the PM pain reliever (21.3 %, $p<0.001$).

In bivariate analyses, prior heavy acetaminophen use and receiving care at a community clinic were significantly associated with exceeding the maximum daily dose on single OTC acetaminophen product. These factors and also older age, male gender, black race, less education, lower

Table 1. Sample Characteristics (N=500)

Variable	Total %
Age, mean (SD)	49.3 (14.8)
Female	62.6
Race	
White	34.0
Black	56.8
Other	9.2
Education	
High School or less	38.6
Some college	23.0
College grad	38.2
Income	
<$20,000	35.8
$20,000–$50,000	27.5
>$50,000	36.7
Literacy Level	
Limited (< 9th grade)	38.7
Adequate (≥ 9th grade)	61.3
Acetaminophen Use	
None	43.8
Moderate	37.6
Heavy (> 2 times/week)	18.6

Table 2. Rates and Types of Dosing Errors for Over-the-Counter Products Containing Acetaminophen

Error Rates, %	Medicine Type mg of acetaminophen per recommended dose (instructions)			P value
	250 mg Tablets (500 mg dose; 2 every 6 hours)	500 mg Gelcaps (1000 mg dose; 2 every 4–6 hours)	650 mg Caplets (1300 mg dose; 2 every 8 hours)	
Exceeded max dose in 24 hours	6.0*	17.5	11.4	<0.0001
Common errors†				
Too many pills per dose	5.0	4.0	3.1	0.18
Interval between doses too short	23.5	6.7	38.3	<0.0001
Too many doses per/day	7.1	21.8	17.1	<0.0001

**Recommended maximum daily dose of this product is not based on acetaminophen but on other active ingredients; max dose results in 2000 mg of acetaminophen*

†Reflects errors made by patients, regardless of whether this resulted in exceeding max dose in 24 hours. Patients may have also made more than one of these errors

Table 3. Percent of Patients Double-Dipping on Acetaminophen-Containing Medicines

Base Product	% Indicating it is Safe to Take Max Dose of Base Product + Second Acetaminophen Product (below)				P Value
	Generic Arthritis Pain Reliever (1300 mg/dose)	Brand Name PM Pain Reliever (1000 mg/dose)	Brand Name Combination Pain Reliever (500 mg/dose)	Brand Name Combination Cold & Cough (650 mg/dose)	
Brand Name Pain Reliever (500 mg per gelcap; 2 every 4–6 hours)	11.6	21.7	11.0	20.1	<0.0001
Brand Name Combination Sinus Congestion & Pain Reliever (325 mg per caplet; 2 every 4 hours)	12.6	21.3	11.5	12.1	<0.0001

income, and limited literacy were associated with double-dipping (Table 4). In multivariable analyses, limited literacy (relative risk ratio (RR) 1.65, 95 % confidence interval (CI) 1.03–2.66), heavy acetaminophen use in the past six months (RR 1.70, 95 % CI 1.10–2.64), and receiving care at community health centers (RR 1.81, 95 % CI 1.05-3.11) were all significant independent predictors of overdosing single ingredient, acetaminophen non-prescription products (Table 5). African American patients were less likely to overdose these drugs within a 24-hour period compared to white patients (RR 0.46, 95 % CI 0.28-0.76). For the outcome of double-dipping, patients with less household income (RR 1.96, 95 % CI 1.03–3.72) and reporting heavy acetaminophen use (RR 1.42, 95 % CI 1.02–1.98) were more likely to report it would be safe to simultaneously use two non-prescription acetaminophen products. Female patients were less likely to double-dip compared to male counterparts (RR 0.64, 95 % CI 0.49–0.83).

Table 4. Percentage of Patients Overdosing or Double-Dipping with Acetaminophen Products, by Patient Characteristics

Variable	Overdose on Single Product (n=119)		Double-Dipping with 2 Products (n=228)	
	%	P Value	%	P Value
Age		0.51		0.05
18-30	18.6		37.1	
31-45	22.0		44.1	
46-60	26.9		52.8	
61-80	23.5		40.0	
Gender		0.23		0.03
Female	22.0		41.9	
Male	26.7		51.9	
Race		0.91		<0.0001
White	24.7		25.9	
Black	23.6		58.8	
Other	21.7		37.0	
Education		0.09		<0.0001
High School or less	29.0		69.4	
Some college	19.1		40.0	
College grad	21.5		25.1	
Income		0.66		<0.0001
<$20,000	26.6		68.2	
$20,000-$50,000	23.3		45.9	
>$50,000	22.6		23.2	
Literacy Level		0.15		<0.0001
Limited	27.1		64.6	
Adequate	21.4		34.2	
Acetaminophen Use		0.02		<0.0001
None	22.8		41.6	
Moderate	19.7		41.0	
Heavy	34.4		64.5	
Clinic Type		0.04		<0.0001
Academic	19.9		28.3	
Community	27.7		63.1	

DISCUSSION

Nearly one in four patients in our sample demonstrated they would exceed recommended amounts of acetaminophen on one or more common OTC products, and 5 % dosed out amounts that could cause serious harm (> 6 grams). In addition, nearly half of patients would overdose by double-dipping with two OTC medications containing acetaminophen. To our knowledge, this study is the most extensive investigation of adults' ability to safely dose OTC analgesic products. Our findings suggest that many consumers do not recognize or differentiate the active ingredient in OTC pain medicines, nor do they necessarily closely adhere to package or label instructions. Given the prevalence of the problem, risk of significant adverse effects, and lack of a learned intermediary to guide decision making and counsel consumers on proper use, we believe this to be a serious public health threat requiring urgent attention.

Beyond the prevalence of overdosing OTC acetaminophen medications, either alone or by double-dipping with multiple products, our study elucidates the possible root causes that can be attributed to specific products. For example, when participants were asked to dose out single OTC medications, they were more likely to exceed the maximum daily dose (4 grams) with the 1000 mg/dose product (17.5 %), and least likely with the 500 mg/dose medicine (6.0 %). This could be attributed to either the product's higher dosage (500 mg vs. 250 mg per pill), more ambiguous directions, or simply instructions that allow you to exceed the maximum daily dose by too many doses per day (2 pills every 4–6 hours vs. 2 pills every 6 hours).

Demonstrated overdose associated with double-dipping was far more common than what was seen with single product use. Looking closely at Table 3, it would appear that a likely explanation could be a greater reliance on

Table 5. Predictors of Overdose and Double-Dipping with Acetaminophen-Containing Products

Variable	Overdose			Double-Dipping		
	RR	95 % CI	P Value	RR	95 % CI	P Value
Literacy						
Adequate	1.00			1.00		
Limited	1.65	1.03–2.66	0.04	1.23	0.90–1.68	0.19
Age (years)	1.00	0.99–1.02	0.45	1.00	0.99–1.01	0.61
Female	1.02	0.72–1.45	0.90	0.64	0.49–0.83	0.001
Race						
White	1.00			1.00		
Black	0.46	0.28–0.76	0.002	1.36	0.86–2.15	0.19
Other	0.68	0.33–1.42	0.31	1.25	0.67–2.33	0.48
Household Income						
>$50,000	1.00			1.00		
$20,000–$50,000	1.00	0.60–1.65	0.99	1.46	0.84–2.53	0.18
<$20,000	0.91	0.49–1.68	0.75	1.96	1.03–3.72	0.04
Acetaminophen Use						
No use	1.00			1.00		
Moderate	0.83	0.56–1.24	0.37	1.16	0.86–1.58	0.33
Heavy	1.70	1.10–2.64	0.02	1.42	1.02–1.98	0.04
Clinic Type						
Academic	1.00			1.00		
Community	1.81	1.05–3.11	0.03	1.13	0.67–1.89	0.65

indication for use versus, especially when considering multiple product use. The indication (i.e. headache, fever, pain, cold, sleep, etc.) of an OTC medication might be more recognizable to individuals than what the product contains. Rates of double-dipping were highest between a pain reliever medication and PM pain reliever (21.7 %), pain reliever and cold and cough medication (20.1 %), and sinus medication and PM pain reliever (21.3 %). Even though the active ingredients in each product are stated on the package and bottle labels, it could be that the symptom relief advertised on the product suggests to consumers that products contain different medicine, and that dual use might be safe.

Not surprising, participants with lower literacy were at greater risk of overdose. Prior research examining medication misunderstanding, use and non-adherence to prescription and non-prescription drugs have reported similar findings.[23–26] Our study provides additional evidence of the problem of confusing OTC medication labeling, especially for the large proportion of Americans who have inadequate health literacy skills. Interestingly, we also found that one in five adults in our sample self-reported heavy acetaminophen use over the past six months. These individuals were more likely to overdose and double-dip with OTC acetaminophen products. It is important to not only communicate to consumers what is in a particular product, but to more adequately convey that they should seek out medical consultation if they exceed a certain period of extended use.

Clearly, our study is limited by the fact that the assessments of individuals' misunderstanding and misuse of OTC acetaminophen products reflects hypothetical and not actual health behaviors. It is possible that participants might have applied greater effort to the tasks if they had been actually experiencing symptoms that would call for these medications. However, it is also reasonable to suggest that our estimates of overdosing and double-dipping are conservative. Participation in the study itself might have generated greater awareness to OTC active ingredients and directions, thereby optimizing task performance. Similarly, if individuals were not acutely in pain or experiencing other symptoms at the time of the interview, they would feel less urgency and distraction, and likely make fewer errors compared to a real-life situation.

We also did not have information regarding patients' comorbidity, especially around clinically relevant conditions such as hepatitis, cirrhosis, or alcohol addiction. This information would have been useful in further understanding the associations between unintentional misuse and adverse outcomes. A final limitation to our study for mention would be the possibility of regional differences as cause for active ingredient confusion and product misuse. In Atlanta and less so in Chicago, our previous investigation found differences between these two cities and among these patient populations around commonly-used, non-prescription acetaminophen products. While we were able to account for socioeconomic status, literacy, and other demographic characteristics, it could be possible that additional, unmeasured regional or cultural factors could have contributed to patient misunderstandings.

As of April 29, 2010 the FDA required labeling on all acetaminophen-containing products to have the active ingredient prominently identified on the product's principal display panel.[27] In addition, new warnings were required in a product's "Drug Facts" label to highlight the potential for liver toxicity from either 1) taking more than the recommended dose of acetaminophen, 2) using more than one product containing acetaminophen, and/or 3) taking acetaminophen with moderate amounts of alcohol. Further, in Fall 2011 the leading manufacturer of acetaminophen made changes to the labeling of its extra-strength acetaminophen

(500 mg per pill) products. It now indicates a maximum recommended dose of six pills—or three grams—with a dosing interval of 6 hours versus the 8 pills (four grams) with a dosing interval of 4–6 hours previously recommended.[28] This is further supported by the National Coalition of Prescription Drug Programs (NCPDP), which should aid the dissemination of these requirements to other acetaminophen manufacturers.[29] Based on our findings, these efforts appropriately targeted the OTC product with the greatest risk for consumer overdose. And based on a prior study by King and colleagues, increasing awareness of the dangers of liver toxicity with acetaminophen use is clearly a public health goal.[3]

However, it is likely that additional public health education efforts will be needed to address longstanding beliefs around OTC use given the high prevalence of overdosing in our sample, lack of clarity around active ingredient, and failure to closely adhere to label directions. As many consumers will have extensive prior experience with these OTC products and may no longer closely attend to label instructions, proposed label changes alone may be ignored. The challenge will be to adequately educate the public that there are potential safety hazards of using OTC products, and it is important to always 1) know the active ingredient of an OTC medicine, 2) closely read and follow directions, 3) attend to any label warnings or precautions. Further research is also needed to determine if the problem, especially double-dipping, is as prevalent or worse among those receiving prescription drugs that contain acetaminophen.

Advertising for OTC products has Federal Trade Commission (FTC), rather than FDA oversight, and OTC medicines are not required by the FTC to state active ingredients in print and media.[29] Thus, consumers are not as often exposed to what the 'active ingredient' of an OTC product means, and its importance for the safe and effective use of a medication. Aligning the oversight of FTC with that of the FDA could allow for more opportunities to educate the public on the importance of understanding active ingredient and maximum daily dose information to reduce errors and serious harm associated with OTC products. There are also ongoing opportunities that could impact label standards, promote consumer education, and establish health policies to reduce unintentional misuse of OTC medications containing acetaminophen. In 2010, the Food and Drug Administration (FDA) announced its Safe Use initiative; a public and private collaboration to coordinate efforts around improving medication safety.[30] Similarly, the Centers for Disease Control since 2008 has engaged its PROTECT initiative, to bring together industry, academia, and government to the unified goal of reducing medication errors and adverse events associated with OTC and prescription medications, particularly among children.[31] We hope our study findings can aid these efforts by drawing attention to the extent of the problem and who is at risk, and how variations in product instructions and labeling might be part of the problem, highlighting the need for explicit consumer education. Research linked to the CDC PROTECT initiative has already examined how parents may have difficulty dosing OTC pediatric liquid products; further investigation based on our findings might seek out knowledge of the active ingredient for these products, as a matter of pediatric patient safety.[32]

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Conflict of Interest: *Drs. Wolf and Davis have previously provided research consultation services (health literacy, study design for comprehension testing for OTC product use) for McNeil Consumer Healthcare. Dr. Wolf and Stacy Bailey are Consultants to Abbott Labs. All other authors declare they do not have a conflict of interest.*

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