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ORIGINAL REPORT

Patterns of acetaminophen medication use associated with exceeding the recommended maximum daily dose

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ABSTRACT

Background Acetaminophen overuse has been linked to liver injury.
Purpose To identify patterns of medication use associated with exceeding the recommended daily maximum dose of 4 g acetaminophen.
Methods Respondents from a national panel completed a detailed daily medication diary online for 7 days ($n = 5649$), identifying medications taken from a comprehensive list of over-the-counter (OTC) and prescription (Rx) acetaminophen medications. Respondents were not told the study concerned acetaminophen. Total daily intake was calculated from diary data. Generalized estimating equations assessed the association of medication patterns with exceeding 4 g per day among 3618 respondents who used acetaminophen medications (on 13 852 days) during the diary period.
Results Acetaminophen intake exceeded 4 g on 3.1% of usage days; median intake on those days was 5.5 g. As expected, days when intake exceeded 4 g were almost always (92%) marked by deviations from label directions—exceeding the one-time dose, re-dosing too soon, and concomitant use of multiple acetaminophen medications. Re-dosing too soon was the most frequent deviation, and concomitant use was most strongly tied to exceeding the daily limit. Use of both an Rx and an OTC medication on the same day also increased the odds of exceeding 4 g on days when concomitant use occurred.
Conclusions Excess dosing of acetaminophen is associated with deviations from label directions and by use of both OTC and Rx medications containing acetaminophen within a single concomitant use day. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—acetaminophen; dosing behavior; survey research; epidemiology; drug safety; pharmacoepidemiology

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Acetaminophen is a widely used medication present in hundreds of over-the-counter (OTC) and prescription (Rx) medications indicated for pain or fever as well as symptoms associated with colds, flu, and allergies. It is considered safe when dosed as directed but, in high doses, has been associated with liver injury, and overuse is reported to be responsible for over 10 000 emergency room visits annually in the USA.[1] Most acetaminophen-attributed liver injury is due to intentional self-harm and associated with high doses,[2–4] but other cases are due to inadvertent overdosing. Although retrospective cases have reported liver injury at recommended doses, acetaminophen is considered safe when used as directed.[5–7] A daily dose of 4 g provides a margin of safety[7] and has been the recommended maximum on OTC medication labels,[8] although lower doses may be recommended by some healthcare providers for certain patients (e.g., those with known cirrhosis).[9] Concern about acetaminophen-associated harm led the US Food and Drug Administration to convene an Advisory Committee in 2009 to recommend actions to reduce liver injury attributed to excess ingestion of acetaminophen.[10,11]

Food and Drug Administration's review of acetaminophen medications[12] raised particular concerns about OTC combination medications in which acetaminophen is combined with other ingredients to

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address multiple symptoms of cold, flu, allergy, and/or sleeplessness, because consumers might fail to note the presence of acetaminophen and thus inadvertently increase their acetaminophen intake by concomitantly using multiple acetaminophen medications. Similar concerns were raised about Rx analgesics combining acetaminophen with opiates, which constitute the most prescribed category of drugs in the USA.[13] The Advisory Committee recommended withdrawing such Rx combination medications from the market.[14]

Acetaminophen doses exceeding the recommended daily maximum of 4 g are seen in medical settings among 6.6% of inpatients,[15] on 2.6% of days,[16] and among 15.1% of outpatients prescribed opiate combinations, on 7.2% of days of opiate use.[17] However, detailed prospective data on patterns of use of both OTC and Rx medications by consumers, including excess consumption, have been lacking. We previously reported results from a population study of acetaminophen use, finding that 4.5% of acetaminophen users took more than 4 g on at least 1 day during a 7-day diary period (with 1.2% exceeding 4 g on 4 or more days).[18] Those who exceeded this limit were more likely to have chronic pain, frequent healthcare visits, attitudes that promote overuse, and limited knowledge both of acetaminophen as an ingredient in their medications and of proper dosing of acetaminophen medications. Chronic pain and mental health diagnoses were also identified as risk factors in a study of US veterans.[19] This informs our understanding of "who" exceeds acetaminophen-dosing limits but does not shed light on "how" such overdoses happen. Accordingly, this paper delves into that dataset to examine the within-day patterns of use associated with exceeding 4 g on that day. As label directions are the primary way of directing consumer behavior towards safe use, particularly for OTC medicines, we examine what role deviations from these directions play in excess dosing. We also examine whether specific medication types, or combinations of medication types, are associated with exceeding the daily maximum dose.

METHODS

The study, fielded 28 July–3 September 2010, was ruled exempt by the Boston University Medical Campus Institutional Review Board. The methods have been described in detail elsewhere.[18]

Participants

Respondents were drawn from an internet panel of 1 500 000 research volunteers maintained by Lightspeed, Inc. E-mails sent to adults (age ≥18 years) sampled randomly from the panel invited them to a website to learn about the study and enroll in return for points that could later be redeemed for goods. Neither the invitation nor the enrollment script (nor any later communication) indicated that the study was about acetaminophen. The demographic profile of invitees was adjusted as needed to recruit a sample matching the US population. Only news reporters were excluded from enrollment. About half the sample was enrolled without restriction; an additional, "enriched" sample was restricted to respondents who reported using an acetaminophen medication in the past 30 days, to increase the proportion of respondents who would use acetaminophen during the observation period.

A total of 215 122 invitations were sent (it is not known how many were received or viewed), 47 738 persons visited the enrollment website, and 5649 completed the study, defined as completing seven consecutive diary days and an exit questionnaire. The median age was 49 years, and the sample was 56% female and 18% non-white; 44% reported income below $50 000; and 82% had progressed beyond high school. The sample roughly matched the demographic and regional profile of the US population, with the notable exception of under-representing those with low income and low educational attainment (see Kaufman *et al.*[18] for detailed comparisons). The analysis focused on 3618 completers whose diaries indicated use of acetaminophen medication on at least one occasion.

Data collection

After an initial enrollment questionnaire, respondents were prompted by e-mail daily for up to 10 days to complete an online diary of medication use, with the aim of collecting diaries for 7 consecutive days. Each evening, respondents reported medications they had taken in the past 24–48 h (they were allowed to fill in the previous day's use), indicating how much they had taken and when, using a grid of hours running back to the time they completed the previous diary. To identify medications, respondents selected from a list of 386 acetaminophen-containing medications organized in a hierarchical structure by class (OTC versus Rx), indication (pain/fever, cold/flu, allergy, and sleep), and brand or product name. Respondents were not told that the list was limited to acetaminophen-containing medications. To reduce the burden of finding their medications for each diary entry, participants selected from a personal list of medications on hand, which they had initially created at enrollment, and to which they could add at any time.[18]

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Definition of key variables

The units of analysis were days. For analysis by medication types, we distinguished Rx medications (all combined with other active ingredients, almost always opiates) from OTC medications. Within OTC medications, we distinguished single-ingredient (SI) medications containing only acetaminophen from combination products containing other active ingredients (most commonly antihistamines, decongestants, or expectorants, aiming to treat allergy, cold, or flu symptoms).

The daily intake of acetaminophen was computed from the diary data to identify days (midnight to midnight) on which the recommended maximum daily dose of 4 g acetaminophen was exceeded.[18] Three other deviations from the OTC label directions were identified from diary records. Exceeding the one-time dose ("too much"): taking more than the label-directed dose for a single occasion. Because the one-time dose prescribed for Rx medications was unknown to us, these medications were never considered to exceed the one-time dose. Re-dosing too soon: taking a subsequent dose of a given medication sooner than the minimum recommended interval. For OTC medications, the interval was determined by the label. For Rx medications, a standard 4-h dosing interval was used. We also assigned a 4-h re-dosing interval to OTC medications with a 24-h dosing interval, as the longer interval was based on considerations other than acetaminophen use (e.g., limiting the use of sleep medications to once daily). Concomitant use: taking a second acetaminophen-containing medication within the dosing interval of the first (the label directs users not to use one acetaminophen medication with another). Dosing too soon and concomitant use were defined without reference to amount taken and could occur as a result of dosing across calendar days (e.g., taking one medication at 11 PM and another at 1 AM). For OTC medications where the one-time dose or dosing interval was not known (usually because they were unbranded generics), the values were imputed based on the medication class; a total of 10% of medications had their dose or dosing interval imputed.

Statistical analysis

The dataset consisted of 13 852 acetaminophen usage days, encompassing 25 878 dosing occasions (a particular medication taken at a particular hour) reported by 3618 study completers who used acetaminophen during the diary period. Because days with only one dosing occasion were unlikely to include concomitant use or dosing too soon, analyses were also performed on a subsample of 6211 days with two or more dosing occasions. Analyses of days on which two product types were used were subsequently stratified by whether concomitant use had occurred, to assess whether concomitant use accounted for the effect of the combination. Because respondents could contribute multiple (and varying) days and occasions to the analysis, we used generalized estimating equations (GEE),[20] with an exchangeable correlation structure, to accommodate the nesting of multiple observations within a respondent. Raw percentages are reported for descriptive purposes, accompanied by odds ratios and confidence intervals estimated by GEE, which often differ from those implied by the raw data.

RESULTS

As shown in Table 1, OTC medications were the most commonly taken: OTC SI and OTC combinations were each taken on over 40% of usage days; Rx medications were taken on 22% of days.

Deviations from label directions

Intake of acetaminophen exceeded 4 g on 3.1% of usage days ($n=431$); on those days, the median intake was 5.5 g. A total of 0.5% of usage days ($n=66$) exceeded 8 g. Table 2 shows that exceeding 4 g was more likely to occur on days when users deviated in other ways from label directions, with each deviation making an independent contribution to the likelihood of excess dosing (multivariate odds ratios 5.4–7.6). Concomitant use had the strongest relationship with exceeding 4 g. In analyses of days with two or more dosing occasions (which are typically necessary for concomitant use and dosing too soon), the effects of concomitant use and dosing too soon remained, although somewhat attenuated. As expected (because it does not require two dosing occasions), the effect of exceeding the one-time dose was unchanged.

Table 3 elaborates this association, showing that 4 g was rarely exceeded unless usage deviated from other label directions: 92% of days exceeding 4 g also had at

Table 1. Medication types used on usage days

Medication type	Number of days	% of days*
Rx	3060	22.1%
OTC	11 593	83.7%
OTC single ingredient	6626	47.8%
OTC combinations	5881	42.5%
Total	13 852	–

Rx, prescription; OTC, over-the-counter.
*Percents indicate the days on which each kind of medication was used, regardless of what else was used. Percents add to more than 100%, because multiple medication types could have been used in a single day.

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Table 2. Likelihood of exceeding 4 g in a day, by deviations from the label directions

Label deviations	Number of days	% of days with deviation	% of days dosing > 4 g*	Univariate OR (95% CI)†	Multivariate‡ OR (95% CI)†
All days§					
Dosed too soon¶	1782	12.9	17.3	7.0 (4.3–11.5)	5.7 (3.8–8.5)
All other days‖	12 070	–	1.0		
Dosed too much¶	855	6.2	17.1	5.8 (3.2–10.5)	5.4 (3.2–9.1)
All other days‖	12 997	–	2.2		
Concomitant use¶	1293	9.3	19.7	8.2 (4.9–13.6)	7.6 (4.8–11.9)
All other days‖	12 559	–	1.4		
Days with ≥2 dosing occasions**					
Dosed too soon¶	1668	26.9	18.5	4.4 (2.8–6.9)	4.4 (3.0–6.5)
All other days‖	4543	–	2.5		
Dosed too much¶	409	6.6	35.7	5.6 (2.8–11.2)	5.1 (2.9–9.0)
All other days‖	5802	–	4.8		
Concomitant use¶	1286	20.7	19.8	4.9 (3.1–7.6)	6.0 (4.0–9.1)
All other days‖	4925	–	3.4		

OR, odds ratio; CI, confidence interval; GEE, generalized estimating equations.
*Percentages based on raw data, which may differ from adjusted estimates used by GEE.
†GEE at the day level, using exchangeable correlation structure.
‡Multivariate models included terms for all three label deviations.
§$n = 13\,852$ days when acetaminophen medications were used.
¶Overlapping categories, separate analyses.
‖"All other days" includes days on which the deviation in the aforementioned row did not occur. Those days could have included other deviations.
**$n = 6211$ days when acetaminophen medications were used on two or more occasions.

Table 3. Other deviations from label directions on days intake exceeded daily maximum dose of 4 g acetaminophen

	Days on which intake exceeded 4 g ($n = 431$)	
	n days	% *
Pattern of deviations		
No deviation	33	7.7
One deviation	124	28.8
Multiple deviations	274	63.6
Specific deviations		
Too soon†	309	71.7
Too much†	146	33.9
Concomitant use†	255	59.2

*Expressed as a percentage of the 431 days when 4 g was exceeded.
†Overlapping samples, as multiple deviation types could occur on a single day.

least one other type of label deviation, and 64% had two or more. Re-dosing too soon and concomitant use were considerably more common than exceeding the one-time dose.

Consumption exceeding 4 g in a day by types of medications used

We examined whether the use of particular medication types was associated with exceeding 4 g (Table 4). The likelihood of exceeding 4 g on Rx-only days did not differ significantly from that on OTC-only days. Compared to days on which only OTC SI medications were taken, the odds of exceeding 4 g were 70% lower on

Table 4. Risk of exceeding 4 g acetaminophen on acetaminophen usage days, by medication types used, all days

	All days on which only one type of medication was used			
Medication type	Usage days	Usage days exceeding 4 g	% exceeding 4 g*	Odds ratio (95% confidence interval)†
Rx only‡	2259	57	2.5%	0.6 (0.3–1.2)
OTC only	10 792	248	2.3%	Reference
Single ingredient only§	5362	139	2.6%	Reference
Combination medication only¶	4603	20	0.4%	0.3 (0.1–0.7)

Rx, prescription; OTC, over-the-counter; GEE, generalized estimating equations.
*Percentages based on raw data, which may differ from adjusted estimates used by GEE.
†GEE at the day level, using exchangeable correlation structure.
‡All Rx medications are combinations, usually combining acetaminophen with an opiate analgesic.
§OTC single-ingredient medications are indicated for pain and fever.
¶OTC combinations are most commonly indicated for cough/cold/flu symptoms, although the category also includes some indicated for pain (combined with other analgesics) or for sleeplessness (combined with sedating ingredients).

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days when only OTC combination medications were used (OR = 0.3, 95% CI 0.1–0.7).

We also examined the likelihood of exceeding 4 g on days when two types of medication were both used, on the 6211 days with at least two medication occasions (Table 5). The odds of exceeding 4 g were significantly higher on days that included both an Rx and an OTC medication, compared to days with only OTC medication(s). When only OTC medications were used, exceeding 4 g was more likely on days that included both SI and combination medications. Use of OTC SI and OTC combinations was no longer significantly associated with exceeding 4 g when days were stratified according to whether concomitant use had or had not occurred. In contrast, the effect of using both an Rx and OTC medication was still associated with a near doubling of the odds of exceeding 4 g on days with concomitant use, although not on days without concomitant use.

DISCUSSION

This was the first study to examine patterns of acetaminophen use associated with exceeding the recommended maximum daily dose of 4 g. The diary data revealed that exceeding 4 g in a day was relatively uncommon, occurring on 3% of usage days, and that doses exceeding twice the recommended maximum occurred considerably less frequently (0.5% of days).

The detailed usage data allowed for a fine-grained analysis of behaviors associated with exceeding the daily maximum dose. A striking finding was that exceeding 4 g was almost always associated with deviations from other label directions, especially re-dosing a medication sooner than directed and/or engaging in concomitant use of multiple acetaminophen medications. It was possible to exceed 4 g without deviating from the other directions, by dosing around the clock (e.g., 1 g every 4 h for 20 h would equal to 5 g), but this accounted for only 8% of days exceeding 4 g. Deviating from any of the key label directions steeply increased the odds of exceeding 4 g (fourfold to eightfold). This suggests that the risk of overdose could be substantially reduced if users could be induced to adhere to the current directions. The proportions of usage days with deviations from label directions ranged from 6.2% for exceeding the one-time dose to double that for re-dosing too soon. These rates were roughly comparable to those observed when clinic patients were asked hypothetically how they would use OTC acetaminophen medications,[21] but the observed rates of concomitant use in our study were much lower than those seen under a hypothetical scenario.

In our diary data, re-dosing too soon was the most common deviation from the label; users may have redosed too soon because their pain or other symptoms returned before the label dosing interval expired. The need for more symptom relief could also have driven concomitant use of multiple acetaminophen medications, which was most strongly related to exceeding the daily dose limit. Avoiding concomitant use also requires that users know which medications contain acetaminophen; it has been suggested that an icon could help identify such medications. In our previous analyses,[18] persons who did not know that their medications contained acetaminophen were more likely to exceed 4 g, as were persons who did not know the dosing directions, suggesting that consumer education could be an important intervention to reduce inappropriate dosing of acetaminophen.

We examined how use of varied medication types within a day related to the likelihood of overdose. On days when only OTC medications were used, users were much less likely to exceed 4 g when their use was limited to OTC combination medications, compared to days limited to OTC SI medications. OTC SI medications are used primarily for pain, which may provide more

Table 5. Risk of exceeding 4 g acetaminophen on acetaminophen usage days, by combinations of medication types used, days with two or more medication occasions

			Usage days with 2 + dosing occasions $n = 6211$		Stratified by concomitant use			
					Concomitant use		No concomitant use	
Medication type	Usage days	Usage days exceeding 4 g	*n* days	Odds ratio (95% CI)*	*n* days	Odds ratio (95% CI)*	*n* days	Odds ratio (95% CI)*
Both OTC and Rx	801	126	801	2.6 (1.8–3.9)	530	1.8 (1.2–2.6)	271	0.9 (0.5–1.6)
OTC only	10 792	248	4043	Reference	684	Reference	3359	Reference
OTC SI only	5362	139	1825	Reference	64	Reference	1761	Reference
OTC SI + combination	827	89	827	1.8 (1.1–2.9)	444	0.6 (0.3–1.2)	383	0.8 (0.4–1.4)

CI, confidence interval; OTC, over-the-counter; Rx, prescription; SI, single ingredient.
*GEE at the day level, using exchangeable correlation structure.

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compelling motivation to overdose. It is also possible that the other ingredients in OTC combination medications may limit dosing, perhaps due to potential side effects (e.g., sedation due to sedating antihistamines) or rapid relief of non-pain symptoms (e.g., nasal congestion).

Days when either OTC medications or Rx medications were used exclusively had similar likelihood of exceeding 4 g; neither medication type, on its own, inherently conferred greater likelihood of overdose. However, days when both OTC and Rx medications were used were more likely to exceed 4 g, although only on days with concomitant use of medications (i.e., temporally proximal use, within the re-dosing period). Users of both OTC and Rx medications may be treating multiple types of pain or very severe pain, which may lead them to dose excessively. Days when both OTC SI and OTC combination medications were used also were more likely to exceed 4 g, but this is attributable to the increased chances of engaging in concomitant use: The effect disappeared when we stratified by concomitant use. Along with the fact that concomitant use had the strongest independent association with exceeding 4 g, this emphasizes the role of concomitant use in leading to exceeding the daily maximum dose.

A limitation of this study was the use of a sample from an internet panel, which avoided the decreasing representativeness of random digit dialing but raised other questions. Although data from such panels can yield valid population estimates,[22,23] internet users likely do not represent the whole population, and the sample particularly under-represented individuals with limited education and income, who might be particularly likely to dose medication inappropriately,[21] although it was roughly similar to the US population in terms of other demographics.[18] The survey's response rate was also low, which could have biased the sample, although lower response rates are not necessarily associated with bias.[24–26]

The self-report data could be degraded by recall problems, but recall in the diary was typically limited to the past 24 h. It is also possible that users might have failed to report their medication taking when they were in particularly severe pain or very ill, times when they might overuse medication. A tendency for respondents to present themselves positively could have led to under-estimating overdose. However, respondents had little reason to dissemble, particularly as they likely did not know that the survey aimed to assess excess intake of acetaminophen. Further, people are more honest when reporting to a computer than to a person.[27,28] The study was conducted during the summer months, and it is possible that use of OTC medications, especially those intended to treat colds and flu, would be different during other seasons. Finally, this was a study of dosing behavior, and not of medical consequences of acetaminophen use, and we did not assess consequences or consider individuals' medical condition in defining appropriate dosing, focusing on conformity to label directions.

The strengths of the study included collection of highly detailed daily diary data on use of acetaminophen medications from a large national sample. The study methods made it possible to collect data on acetaminophen medications without respondents needing to know which medications contained acetaminophen or even knowing that the study concerned acetaminophen use, which might otherwise have sensitized them about reporting inappropriate use.

SUMMARY AND CONCLUSIONS

This is the first study to characterize patterns of acetaminophen use using detailed hour-by-hour dosing data from daily diaries collected from a wide range of acetaminophen users. The findings add to our prior results[18] by shedding light on particular dosing behaviors associated with acetaminophen consumption exceeding the recommended limit of 4 g in a day. The data identify deviations from label directions as key contributors to exceeding the maximum recommended daily dose of acetaminophen, as well as suggesting that using both an Rx and OTC medication on a concomitant use day may further increase the likelihood of excess dosing. These findings have important implications for the design of interventions to decrease excess use of acetaminophen, particularly suggesting better communication of acetaminophen as an active ingredient and public education to emphasize the importance of heeding the label directions.

CONFLICT OF INTEREST

This research was sponsored by McNeil Consumer Healthcare, which markets Tylenol-brand acetaminophen medicines. Saul Shiffman, Jeffrey Rohay, Deena Battista, and Pinney Associates are consultants to McNeil Consumer Healthcare and other companies that market competing OTC analgesics, including Bayer, Chattem, GlaxoSmithKline, and Pfizer. Judith Kelly has no conflicts to report. Mary Kathryn Malone is a consultant to McNeil Consumer Healthcare. Rachel Weinstein is an employee of Janssen Research and Development, LLC. Both McNeil Consumer Healthcare and Janssen Research and Development are part of Johnson & Johnson. David Kaufman received research support from Bayer during the conduct of the study and has been a consultant to UCB.

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KEY POINTS

- The recommended daily maximum acetaminophen dose of 4 grams (combined Rx and OTC) is exceeded on 3.1% of usage days.
- The median daily dose is 1 gram, and the median daily dose on days exceeding 4 grams is 5.5 grams.
- Exceeding 4 grams in a day is almost always (92%) associated with deviations from other aspects of label directions: exceeding the recommended 1-time dose, re-dosing too soon, and/or concomitant use of multiple acetaminophen medications at the same time.
- Intake is more likely to exceed 4 grams on days when both Rx and OTC medications are used and when concomitant use occurred.
- The data suggest avenues for mitigating acetaminophen overdose by promoting adherence to label directions and limiting use of multiple medications containing acetaminophen.

ETHICS STATEMENT

The study was reviewed by the Boston University Medical Campus Institutional Review Board and ruled exempt.

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