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RESEARCH

Exceeding the maximum daily dose of acetaminophen with use of different single-ingredient OTC formulations

Saul Shiffman*, Deena R. Battista, Judith P. Kelly, Mary K. Malone, Rachel B. Weinstein, David W. Kaufman

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ABSTRACT

Objectives: To assess whether there are differences in the likelihood of exceeding the daily limit of 4 grams of acetaminophen when using different formulations (325 mg, 500 mg, 650 mg) of OTC single-ingredient (SI) acetaminophen medications.

Design and setting: Multiyear observational study of acetaminophen use via daily online acetaminophen-usage diaries completed for 7 days.

Participants: A total of 7579 U.S. adults from online research panels who used acetaminophen in the month preceding enrollment and used an OTC SI acetaminophen medication during the study.

Outcome measure: Exceeding the daily dose.

Results: On days when 325-mg or 500-mg OTC SI formulations were taken, users were not significantly more likely to exceed 4 grams than on days when OTC SI formulations were not used. On days when 650-mg extended-release (ER) formulations were taken, exceeding 4 grams was significantly more likely (8.9% of days vs. 4.4%; $P < 0.0001$; median on those days was 5.2 g) than on days with 325- or 500-mg OTC SI formulations. Users of 650-mg ER formulations were significantly less likely to know their dosing interval of 8 hours (33% vs. 49%; $P < 0.0001$) and more likely to redose too soon (26% vs. 10%; $P < 0.0001$) and to use other acetaminophen medications concomitantly (14% vs. 7%; $P < 0.0001$). These patterns were strongest among 650-mg ER products that did not include "8-Hour" in the product name.

Conclusion: Usage of 500-mg OTC SI acetaminophen formulations does not contribute differently to exceeding dosage compared with other OTC SI acetaminophen formulations. Exceeding 4 grams is more likely when 650-mg ER formulations are used. Improved consumer information on the packages and counseling from pharmacists may help to reduce practices that contribute to exceeding the labeled daily limit of these medications.

Acetaminophen is a widely used analgesic and antipyretic present in hundreds of over-the-counter (OTC) and prescription (Rx) medications indicated for pain and fever as well for symptoms of colds, flu, and allergies. It is considered to be safe when taken as directed, but in high doses it has been associated with liver injury, with overuse reported to be responsible for as many as 50,000 emergency room visits and 10,000 hospitalizations annually in the United States.[1] The minimum dosage at which use of acetaminophen risks liver injury has not been clearly established, but a daily dose of 4 grams has been considered to provide a substantial margin of safety and has until recently been the recommended adult maximum on OTC medication labels.[2] We previously reported on an internet panel survey with the use of daily diaries to collect information on acetaminophen consumption over a 1-week period,[3,4]

Disclosure: Saul Shiffman, Deena Battista, and Pinney Associates are consultants for Johnson & Johnson Consumer and have consulted for other companies that market competing OTC analgesics. Mary Kathryn Malone is a consultant to Johnson & Johnson Consumer. Rachel Weinstein is an employee of Janssen Research and Development, which is part of Johnson & Johnson. David Kaufman received research support from Bayer during the conduct of the study and has been a consultant to UCB. Judith Kelly has no conflicts to report.

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* **Correspondence:** Saul Shiffman, PhD, Pinney Associates, 201 N. Craig Street (320), Pittsburgh, PA 15213.

E-mail address: shiffman@pinneyassociates.com (S. Shiffman).

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Key Points

Background:

- Acetaminophen is a commonly used analgesic and antipyretic in both prescription and OTC medications. Many OTC acetaminophen products, and all prescription acetaminophen products, are combinations with other active ingredients.
- Taken in excess amounts, acetaminophen can cause liver injury.
- There has been concern that OTC 500-mg single-ingredient (SI) products might particularly contribute to excess dosing. However, no data have been available to address whether there is any relationship between the various OTC SI formulations (500-mg and 325-mg immediate-release formulations and 650-mg extended-release [ER] formulations) and dosing that exceeds the recommended daily maximum of 4 grams.

Findings:

- The 325-mg and 500-mg immediate-release formulations were not differently associated with exceeding the 4-gram daily limit.
- However, use of OTC 650-mg ER formulations was associated with increased likelihood of exceeding the daily limit, partly owing to inadequate knowledge of the correct 8-hour dosing interval, which was better for ER products that explicitly included "8-Hour" in the product name.
- The findings suggest that OTC SI 650-mg ER acetaminophen medications should prominently call out the 8-hour dosing interval. They also imply that pharmacists should particularly educate users of these 650-mg ER medications regarding the longer dosing interval and the importance of complying with that and all other dosing directions.

with exceeding the 4-gram daily limit as the primary end point. We found that 6.3% of participants who used acetaminophen during the diary week took more than 4 grams on at least 1 day, with 3.7% of usage days exceeding 4 grams.[5]

With the aim of reducing the frequency of excess dosing of acetaminophen, the U.S. Food and Drug Administration (FDA) required manufacturers of Rx combination medications (opiates plus acetaminophen) to reduce the acetaminophen dose to 325 mg or less per tablet.[6] The FDA also changed the label on OTC immediate-release single-ingredient (SI) products to designate 3 grams as the recommended daily maximum dose. OTC acetaminophen medications are also available in combination with other ingredients (usually for upper-respiratory or allergy symptoms or sleeplessness), but these are associated with a lower risk of exceeding the daily 4-gram limit than the SI medications,[7] although subsequent research suggests that they contribute to increases in exceeding 4 grams during cold and flu season.[5] In the United States, OTC SI acetaminophen medications are offered in 3 major formulations: 325- and 500-mg immediate-release, and 650-mg extended-release (ER). Although the 650-mg ER formulations contain more acetaminophen, they release acetaminophen more gradually and are labeled for use every 8 hours, in contrast to the 4–6-hour dosing interval of the immediate-release formulations. The FDA expressed concern that the 500-mg "extra strength" OTC SI formulations, which represent the majority of the usage of OTC SI acetaminophen medications,[7] might particularly contribute to exceeding 4 grams in a day. In 2009 an Advisory Committee recommended, without convincing data to support their position, that the 500-mg dose be available only by prescription,[6] limiting the OTC dose in SI formulations to 325 mg. Although the FDA Advisory Committee raised concerns about the 500-mg dose of acetaminophen in OTC SI products, there are no conclusive data on exceeding the recommended daily dose when different OTC SI formulations are used.

Objective

In the present analysis, we explored whether use of a particular formulation (325-mg, 500-mg, or 650-mg ER) is associated with a greater likelihood of exceeding the 4-gram daily limit.

Methods

This study was deemed to be exempt by the Boston University Medical Campus Institutional Review Board. The study methods have been described in detail elsewhere.[3,4]

Participants

Respondents were adults 18 years of age and older drawn from multiple internet panels of research volunteers maintained by 3 panel companies (Lightspeed Research, GMI, and Survey Sampling International). E-mails sent to random samples of U.S. adult (age $\geq$ 18 years) panel members invited them to a website to learn about the study and enroll. Neither the invitation nor the enrollment script (nor any later communication) indicated that the study was about acetaminophen. The demographic profile of invitees was periodically adjusted to target nationally representative demographics. Respondents were selected for participation on the basis of having used an acetaminophen-containing medication in the past 30 days to enrich the sample with individuals likely to use acetaminophen during the diary period.

Data collection

The present analyses focus on data collected from March 2011 to July 2015, at which time the packaging of Tylenol Arthritis 650-mg products was changed (based on preliminary results from this study) to emphasize the 8-hour dosing interval. After an initial enrollment questionnaire that included reporting on past-30-day acetaminophen use (as described below), respondents were prompted by e-mail daily for 7 days to complete an online diary of medication use. Each day after 3:00 pm, respondents reported the medications they had