Review of Recent Changes to Acetaminophen Products

Over 40 percent of adults in the United States consume at least one over-the-counter (OTC) medication regularly, and more than half of older adults concurrently take five or more prescription and OTC products. With the large number of medications consumed by patients and ease of accessibility of OTC products, conscious efforts must be made to ensure patient safety. For example, only 20 percent of patients report reading product labels for medications, indicating most patients do not receive validated information from any source about their medications. Patients should be better informed about their medications in order to protect themselves. Likewise, it is essential for patients to stay current with drug safety information and protect themselves from unintentional drug injury. However, with frequent product labeling changes and with some medications in short supply, consumers may find it difficult to stay informed and to know what to do in order to safely take...
their medications. Therefore, consumers may require additional assistance to ensure safe and responsible use of their medications.

As the primary medium by which patients purchase medication, pharmacies provide a unique opportunity to educate patients, and many pharmacists take advantage of the opportunities. Although a number of pharmacies provide signage and patient handouts when important product changes occur, many patients may not fully understand the importance of this safety information or notice this signage at all. For instance, 54 percent of patients misunderstand the auxiliary labels accompanying their medications. Additionally, 46 percent of patients misinterpret one or more dosing directions, regardless of the patient’s literacy level. Therefore, pharmacists, technicians, and other pharmacy personnel can and should play an important role in preserving patient safety by warning patients of serious adverse drug reactions and other safety concerns.

Acetaminophen (APAP), the active ingredient in Tylenol® and various other cough and cold products, is the most commonly used medication in the United States, and is available in many prescriptions and OTC products. Nineteen percent of U.S. adults surveyed reported taking APAP in a given week. In 2008, 24.6 billion doses of APAP were sold. Seventy-nine percent of APAP purchases were for OTC products, and 69% were for multiple ingredient combination products. Additionally, 200 million prescriptions were written for prescription APAP-containing products. These prescription products included combinations with hydrocodone, oxycodone, and codeine, as well as tramadol and caffeine/butalbital (table 1). APAP is an effective analgesic and antipyretic, commonly used to relieve mild pain and fever in the treatment of patients of all ages. When used at therapeutic doses, APAP is a safe and effective medication. However, due to the wide variety and availability of APAP-containing products, unintentional overdoses may frequently occur. As such, APAP is the most common cause of acute liver failure in the United States. In 2009, 401 deaths were attributed to APAP or an APAP-containing combination product. Over one-third of those patients who unintentionally overdosed were taking more than one APAP product at the same time.

APAP is metabolized through two distinct pathways in the body (figure 1). Through one of those pathways, ten percent of APAP is converted to a toxic metabolite called N-acetyl-p-benzoquinone imine (NAPQI). Under normal conditions, this toxic metabolite is detoxified into nontoxic byproducts through a metabolic process called glutathione conjugation. In cases of APAP overdose (doses greater than 4g/day), the body’s ability to detoxify NAPQI is overwhelmed and thus this toxic substance remains in the body subsequently resulting in liver injury. NAC works by replenishing glutathione and thereby allowing the detoxification process to resume. Administration of NAC must occur promptly within 12 to 24 hours, before liver cells are damaged by NAPQI and subjected to irreversible oxidative stress and cell death. Unfortunately, APAP overdose often proceeds undetected until symptoms present and damage to the body begins. The longer the body endures APAP damage before receiving NAC, the longer it takes for glutathione stores to be replenished and therefore for NAPQI to be removed from the body. Despite the availability of an antidote, the urgent need for therapy makes it difficult to save all patients who are admitted to the emergency department with APAP poisoning.

Role of the Food and Drug Administration and Consumer Healthcare Products Association

The U.S. Food and Drug Administration (FDA) is responsible for assuring that drugs and vaccines, amongst a number of other products, are safe and effective for human use. Particularly, the FDA’s Center for Drug Evaluation and Research (CDER) ensures drug safety through premarket review and post-market monitoring. In recent years, CDER has made significant contributions to enhancing post-market safety decisions. CDER is not only delivering more effective drug safety

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**Table 1; Common Drugs that Contain Acetaminophen; adapted from reference 30**

<table>
<thead>
<tr>
<th>Brand Name Product</th>
<th>Active Ingredients</th>
<th>Amount of APAP per Usual Adult Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Over-the-Counter Nonprescription</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tylenol® Cold Multi-Symptom Daytime</td>
<td>Acetaminophen, dextromethorphan, phenylephrine</td>
<td>650mg</td>
</tr>
<tr>
<td>Dayquil® Cold &amp; Flu</td>
<td>Acetaminophen, dextromethorphan, phenylephrine</td>
<td>650mg</td>
</tr>
<tr>
<td>TYLENOL® Cold &amp; Cough Nighttime</td>
<td>Acetaminophen, dextromethorphan, phenylephrine</td>
<td>650mg</td>
</tr>
<tr>
<td>Nyquil® Cold &amp; Flu</td>
<td>Acetaminophen, dextromethorphan, doxylamine</td>
<td>650mg</td>
</tr>
<tr>
<td>Robitussin® Peak Cold Nighttime Relief</td>
<td>Acetaminophen, phenylephrine</td>
<td>650mg</td>
</tr>
<tr>
<td>Excedrin® Sinus Headache</td>
<td>Acetaminophen, phenylephrine</td>
<td>650mg</td>
</tr>
<tr>
<td><strong>Prescription</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vicodin®</td>
<td>Hydrocodone, acetaminophen</td>
<td>500mg - 1000mg</td>
</tr>
<tr>
<td>Vicodin® ES</td>
<td>Acetaminophen, tramadol</td>
<td>650mg</td>
</tr>
<tr>
<td>Ultracet®</td>
<td>Acetaminophen, tramadol</td>
<td>650mg</td>
</tr>
<tr>
<td>Percocet®</td>
<td>Oxycodone, acetaminophen</td>
<td>325mg - 1000mg</td>
</tr>
</tbody>
</table>

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**Figure 1; Mechanism of APAP toxicity, adapted from reference 31**
information, but also earlier drug safety information. Drug safety communications provide important safety updates to the public and include major changes to safety labels and new warnings and contraindications for use of medications. Since 2008, each division of the Office of New Drugs at the FDA is also equipped with a deputy director for safety to ensure patient safety pre- and post-marketing.13

The FDA also utilizes various advisory committees in their decision-making processes. Advisory committees consist of a group of outside experts, pharmaceutical industry members and patients/consumers who are able to translate scientific data into public health significance. Committee members come from across the nation and meet together to address and debate important issues. The committees contribute advice to the FDA, and final decisions are determined by the FDA.14

The Consumer Health Products Association (CHPA) is an association of leading manufacturers of nonprescription products who also submits recommendations to the FDA and other government agencies to provide guidance on regulatory and scientific issues.15 CHPA aims to promote the role of nonprescription products and provide safety resources and recommendations. CHPA has launched several initiatives to encourage responsible use of OTC medications. The Know Your Dose campaign16 is one such initiative in which CHPA has partnered with the Acetaminophen Awareness Coalition to increase awareness about using acetaminophen safely and effectively. CHPA has been a leader of change with drug manufacturers to increase safety in the use of APAP containing products.

What Recent Changes Have Been Made to Acetaminophen Containing Products?

Through the years, the FDA has developed various warnings and recommendations for consumers, and in 2007, the Director of FDA’s CDER gathered a group of professionals from varied disciplines to assess all issues surrounding the medication. Various sources were evaluated, and the Director announced that the complex topic would be more appropriate as part of public discussion.17 Below are the topics that FDA’s advisory committees discussed and have been implemented.

Limiting amount of acetaminophen in prescription combination medications

Among unintentional overdoses of APAP, 63% of patients reported using a narcotic/APAP combination product.8 Fifty-six percent of dispensed APAP combination products were for strengths equal to or greater than 500mg of APAP.9 According to various surveys, patients often take multiple APAP containing products and risk unintentionally exceeding the maximum recommended dose of 4,000mg within a 24-hour period.2 As a result, the FDA took action to protect consumers by requesting manufacturers of APAP combination products to limit APAP to no more than 325mg in each tablet or capsule.18 The Federal Register Notice was published January 14, 2011, and drug manufacturers have until January 14, 2013 to implement the APAP limits.19

Boxed warning label

With the established risk of liver damage attributed to APAP use, FDA mandated the inclusion of a boxed warning cautioning about the risk of liver toxicity.20 The boxed warning indicates that “most of the cases of liver injury are associated with the use of APAP at doses that exceed 4000 milligrams per day, and often involve more than one APAP containing product.”18

Patient education becomes increasingly significant with only one in five consumers reading the product label for possible side effects and almost half of participants intentionally taking more than the recommended dose, believing it will increase effectiveness.2 The new drug labels for OTC APAP aim to provide better patient understanding. In one study that compared the old and the new warning labels for OTC APAP and impact on participant perceptions and intentions, after reading the new warning label, 6.3% more participants reported a perceived risk associated with the use of APAP as compared to reading the old warning label. It was shown that the new warning label also elicited a higher level of intentions to protect oneself against APAP-induced liver injury. It is important to note, prior to participation in the study, almost 75% of participants were unaware of changes being made to the product label.2,1

Pediatric liquid products

An additional change implemented for APAP is the consolidation of dosing for pediatric liquid drops. Liquid APAP products were previously available in two concentrations: 160mg/5mL and concentrated 80mg/0.8mL, with unique dosing scales based on age and weight. However, the difference in dosing risked going unnoticed and dosing errors by consumers became a major safety concern. Following almost unanimous support for a single strength of liquid drops in the 2009 Nonprescription Drug, Pediatrics and Drug Safety Advisory Committees meeting, CHPA announced voluntary withdrawal of concentrated infant drops (80mg/0.8mL) in 2011 to reduce the risk of dosing errors. Major manufacturers discontinued production of concentrated infant drops, leaving one standardized liquid APAP concentration (160mg/5mL) using one dosing table based on age and weight, which is the concentration that is traditionally used in children’s APAP products. With accidental unsupervised ingestion being the main cause of overdose, new infant products will also be produced with flow restrictors.22,23

Another safety concern is that almost all OTC liquid formulations have historically displayed inconsistency and variability in packaging and dosing devices.24 Major problems have included: lack of dosage delivery device included, delivery device missing necessary markings, markings on the device not matching what is on the label, and inconsistent use of decimals and fractions.

CHPA voluntarily addressed the issues with packaging improvements: (1) Infant drops will be sold with oral syringes.
Pediatric products will be available with calibrated dosing cups. Doses will be provided in a chart format. Labels will indicate that medication should be taken only with the accompanying measuring device.

Case 1 - Accuracy Measurement

LS brings her crying 6-year-old daughter into the pharmacy and asks for a tablespoon to measure liquid acetaminophen. Her daughter currently has a fever and was refusing acetaminophen drops. The daughter's refusal caused the dropper to slip from LS's fingers and the dropper fell on the floor. Which of the following actions should the pharmacy staff take? Please select the most appropriate answer:

A) Tell LS that she can use the cap on the medication bottle to measure how much acetaminophen to give
B) Give LS a tablespoon so she can measure how much acetaminophen to give
C) Give LS a calibrated medicine dropper instead

The most appropriate answer is C. Measuring devices should be marked with calibrated units of measure. Neither the cap on the medication bottle nor a tablespoon utensil provides a calibrated unit of measure.

Changes proposed by FDA Advisory Committees

Although the changes discussed above have already been made to acetaminophen products, many other questions regarding the use of APAP continue to be discussed and debated. During the FDA's Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee meeting on June 29 and June 30, 2009, members discussed and evaluated issues surrounding APAP-related liver injury. Both OTC and prescription products were addressed. The advisory committees considered the benefits of APAP as an effective treatment of pain and fever while also evaluating actions to improve the safety profile of APAP.

Nonprescription single and combination products

When McNeil, a major manufacturer of APAP, voluntarily reduced the maximum total daily dose to 3000mg on its 500mg APAP products, McNeil's goal was to help promote appropriate APAP use and diminish the risk of accidental overdose. However, as a result, confusion ensued amongst consumers since other brands of APAP persisted with the 4 grams/day maximum. In at least two studies, patients consuming up to 4000mg of APAP daily did not develop liver toxicity. In one retrospective case review, of all patients consuming 4000mg/day or less of acetaminophen, none were identified with liver damage. McNeil's acetaminophen product continues to display a maximum of 3000mg daily dose, while other companies offer products with a 4000mg maximum daily dose. Arguments against the change focus on studies demonstrating hepatic remodeling, sometimes shown in inflammatory processes, or the liver following APAP-induced injury. The processes include growth factor involvement and macrophages clearing out death-inducing necrotic cells, leading to liver regeneration. Should a consumer pose questions regarding the distinction, pharmacy staff may alert the patient of the ongoing debate and inform the pharmacist if further questions need to be answered.

Maximum nonprescription single adult dose

The maximum nonprescription single adult dose, which is currently set at 1000mg, was another topic of debate. With 48% of patients surveyed exceeding the recommended dose of OTC medications and 32% of those consumers intentionally doing so in a single dose, APAP overdosing is a large concern. Having single adult doses of 1000mg retains a relatively high risk of unintentional overdose, especially considering a daily maximum of four times that amount. The FDA's advisory committees debated whether the maximum nonprescription single adult dose should be thus lowered to 650mg. If this change were to take place, 500mg APAP tablets would no longer be available OTC thereby, patients' risk of unintentional overdose may be decreased. By leaving only the 325mg APAP tablets available OTC, the consumption of two additional tablets, on top of the usual adult dose of two 325mg tablets, would need to occur before exceeding the current recommended maximum single adult dose of APAP. At this time, no changes have been made with respect to the maximum nonprescription single adult dose.

Switching current maximum dosage of acetaminophen (2 x 500mg) to prescription status

The Advisory Committees also discussed if the current maximum dosage of APAP (two tablets of 500mg) should be switched to prescription status. A majority of committee members supported the recommendation but did not consider it a high priority because patients are currently able to take 1000mg of APAP safely. Support was met with opportunities for the practitioners to discuss liver toxicity with the patient. However, opposition was explained by reduced accessibility for consumers seeking appropriate pain relief. At this time, no changes have been made.

Changes to packaging of nonprescription acetaminophen products

The Advisory Committees discussed limiting package sizes for OTC APAP products. In line with the concerns regarding maximum single dosages of APAP, smaller package sizes of nonprescription APAP may possibly discourage patients from overusing the medication. Approximately two percent of patients are able to correctly identify the maximum daily dose of regular APAP. Keeping in mind the consistent number of patients admitted to the hospital for APAP-induced liver failure, it is increasingly evident that patients require additional measures to protect their safety with drug products. The discussion closed with a split vote and has not led to any action on this issue.

Elimination of nonprescription acetaminophen combination products

With the concern of therapeutic duplication, possibly leading to APAP overdose, elimination of nonprescription APAP combination products was also addressed. A majority of members opposed this change, emphasizing the importance of nonprescription APAP combination products to provide multimodal therapy with ingredients not necessarily avail-
able individually. Members of the committee recommended alternative action to develop specific use categories for APAP containing products and to label each product with multiple uses if multiple active ingredients are present. As an example, DayQuil® Cold & Flu Relief LiquiCaps® contains the active ingredients APAP, dextromethorphan and phenylephrine. Instead of the label indicating “Cold & Flu,” as it does now, with the proposed change, this DayQuil® would indicate “pain reliever/fever reducer, cough suppressant, nasal decongestant.” No action has been taken with this issue.

Removal of prescription acetaminophen combination products

Prescription products essentially provide safety barriers to patients’ drug understanding through patient contact with the prescribing physician and contact with the pharmacist or pharmacy staff. Still, patients taking prescription APAP products continue to be unaware of the risk of APAP induced liver injury. At this time, the Advisory Committees have already initiated FDA regulations to limit the dose available in combination products to 325mg. Removal of prescription APAP combination products completely was also discussed and elicited a split vote. Opposition arose for the issue with concerns of patients increasing the use of single ingredient opioid products if APAP combination products were taken off the market. At this time, no action has been taken.

Assuming prescription APAP combination products will still remain on the market, “unit-of-use” packaging was also considered. A majority of members voted in support of this change, providing an added barrier to patient overuse of APAP containing products. No action has been taken.

Case 2 - Dosing

MT is a 34-year-old male who is picking up his prescription from the pharmacy for Vicodin® 5/500 (hydrocodone bitartrate 5mg – acetaminophen 500mg) #30 Take 1 tablet by mouth every 4 hours as needed.

When the pharmacy technician rings him up for his purchase, she notices that he wants to purchase DayQuil® Cold & Flu LiquiCaps® along with his prescription medication. She asks if he intends to use the medication together and he answers yes because along with his pain, he is experiencing cold symptoms as well. The technician notices DayQuil® has 325mg of acetaminophen in each LiquiCap® with adult dosing equivalent to 650mg per dose (2 LiquiCaps).

Assuming MT takes the maximum dose allotted for Vicodin® in 24 hours, how much DayQuil® Cold & Flu can MT safely take in that time range? Please select the most appropriate answer.

A) 1 LiquiCap® total in 24 hours
B) 2 LiquiCaps® total in 24 hours
C) 4 LiquiCaps® total in 24 hours
D) 6 LiquiCaps® total in 24 hours

The most appropriate answer is B. The maximum recommended dose of APAP in 24 hours is 4000mg. If MT takes the maximum dose allotted for Vicodin® in 24 hours, MT will consume 3000mg of APAP from Vicodin®. MT can safely take 2 LiquiCaps, bringing the total of APAP to 3650mg in 24 hours. Taking 4 LiquiCaps in 24 hours would exceed the maximum allowable dosage of APAP.

Pharmacy technician’s role

As discussed through this activity, many changes and recommendations surrounding APAP have taken place. Consumers are unlikely to be informed of these safety debates beyond the warnings on package labels, which persist to be unread. All pharmacy staff can contribute to patients’ well-being by pointing out the acetaminophen ingredient in nonprescription combination products. At the frontline of pharmacy interactions, pharmacy technicians may recommend patients to read the labels carefully and use provided dosing devices with pediatric liquids. Pharmacy technicians also importantly assist pharmacists in identifying patients in need of further consultation.

Conclusions

As is evident in the numerous issues addressed by the FDA and its advisory committees, APAP will continue to be a major topic of discussion amongst consumers and pharmacy staff alike. For now, the FDA has limited the amount of acetaminophen found in prescription APAP containing combination products to 325mg and consolidated the strength of over-the-counter pediatric liquid formulations to 160mg/5mL. By being aware of these changes, as well as continued topics of debate, pharmacy technicians will be able to provide knowledge to patients and alert pharmacists for assistance as appropriate.
References:
CPE Instructions:
Pharmacy technicians must read this activity and successfully complete the exam (70% pass rate) and evaluation prior to December 31, 2014 using the following instructions:

- Login to MY PORTFOLIO on www.GoToCEI.org
- On the right of the title of this article, click on GO TO EXAM
- Upon successful completion of the exam, you will see a page with explanations to the exam questions. After reading through this feedback, scroll to the bottom of the page and click GO TO EVALUATION
- Complete the evaluation and click SUBMIT
- You can obtain your CPE Statement of Credit at www.MyCPEMonitor.net within 45 days

If you have any questions about this process, please contact Cindy Smith, csmith@GoToCEI.org, 515-270-8118.

Assessment Questions

1) What toxic metabolite accumulates in an overdose of APAP?
   A) N-acetyl-cysteine (NAC)
   B) N-acetyl-p-benzoquinone imine (NAPQI)
   C) Glutamine
   D) Glutathione

2) How soon after APAP-induced liver injury should the antidote for APAP be administered to patients?
   A) 12 to 24 hours
   B) 96 to 144 hours
   C) 200 hours
   D) 1 to 2 weeks

3) What can technicians do to improve drug safety with APAP? Please select the most appropriate answer.
   A) Remove APAP products from OTC pharmacy shelving.
   B) Provide calibrated dosing devices with pediatric liquid solutions.
   C) Instruct patients with questions about APAP to find answers through a web search.
   D) Require all patients to speak to the pharmacist before purchasing APAP or APAP containing products.

4) What is the maximum daily dose of APAP per the FDA?
   A) 2000mg or 2 grams
   B) 3000mg or 3 grams
   C) 3250mg or 3.25 grams
   D) 4000mg or 4 grams

5) Which organization actively promotes patient drug safety?
   A) U.S. Food and Drug Administration (FDA)
   B) FDA Advisory Committees
   C) Consumer Health Products Association (CHPA)
   D) All of the above.

6) Which of the following ensures drug safety through premarket review and post-market monitoring? This organization also releases drug safety communications to the public.
   A) FDA’s Center for Drug Evaluation and Research (CDER)
   B) FDA Advisory Committees
   C) Consumer Health Products Association (CHPA)
   D) U.S. Drug Enforcement Agency (DEA)

7) According to new changes, what action has the FDA taken to improve patient safety with acetaminophen use?
   A) The current maximum dosage of APAP (2 x 500mg) is now only available by prescription.
   B) The maximum daily dose of APAP is 3000mg.
   C) Combination prescription medications containing APAP can no longer contain 500mg APAP.
   D) Pediatric APAP formulations are available in 2 distinct strengths.

8) How have pediatric doses of APAP been affected by FDA’s improvements in drug safety?
   A) An additional concentration (for a total of 3) of pediatric liquid solutions is now available.
   B) The concentration of pediatric liquid solutions has been standardized to one concentration.
   C) All pediatric doses of APAP have been removed from the market.
   D) All pediatric doses of APAP are now in unit-of-use packaging.

9) What is the new standardized pediatric concentration of APAP?
   A) 80mg/0.8mL
   B) 80mg/1mL
   C) 160mg/0.8mL
   D) 160mg/5mL

10) MT is a 34 year old male who is picking up his prescription from the pharmacy for Vicodin® 5/500 #30 Take 1 tablet by mouth every 4 hours as needed. When the pharmacy technician rings him up for his purchase, she notices that he wants to purchase DayQuil Cold & Flu LiquiCaps® along with his prescription medication. He intends to take them together because along with his pain, he is experiencing cold symptoms as well. The technician notices DayQuil has 325mg of APAP in each LiquiCap with adult dosing equivalent to 650mg per dose (2 LiquiCaps). What should the technician do at this point?
    A) Notify the patient that Vicodin® and DayQuil® both contain APAP and to be careful of dosing.
    B) Offer the patient a consultation from the pharmacist.
    C) Notify the pharmacist that the patient intends to purchase and take DayQuil® in conjunction with Vicodin®.
    D) Ring the patient up and complete his purchase.