



Joint Meeting of the Nonprescription Drugs
Advisory Committee and the Drug Safety and
Risk Management Advisory Committee

FDA Introductory Remarks

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April 4, 2017



Objectives

- Discuss safety issues associated with OTC analgesic combination products used for upset stomach and hangover
 - The monograph permits use of aspirin and acetaminophen in combination with other active ingredients for this indication.
 - The use of single ingredient aspirin, acetaminophen, and bismuth subsalicylate is not today's focus.
- Discuss hangover indication



Antacid-Analgesic Products

- Indicated for minor aches and pains with heartburn, sour stomach, acid indigestion, upset stomach associated with overindulgence in food and drink and symptoms related to hangover



Antacid-Analgesic Products

- The safety of these products has been discussed throughout the rulemaking process
- Aspirin is associated with bleeding risk
 - Reduces cytoprotection of GI mucosa
 - Decreases platelet aggregation
- 21 CFR 330.10(a)(4)(iv) requires that OTC drug combinations provide rational concurrent therapy

Antacid-Aspirin Products

- Antacid and Internal Analgesic Advisory Panels reached different conclusions regarding safety and labeling
- Dosage form limited to solution (unlike antacid-acetaminophen products)
- Deferred to labeling, which has since been revised (i.e., stomach bleeding warning)
- Drug Safety Communication released June 2016

Overindulgence Tentative Final Monograph (12/24/91)

- Amended the Antacid and Internal Analgesic monographs and provided new indications
 - Antacid: Overindulgence in food and drink
 - Antacid-analgesic: Overindulgence in food and drink AND hangover
 - Analgesic-caffeine: Hangover
- Part of effort to establish Overindulgence monograph for symptom-based categories



Hangover

- Advisory Review Panel on OTC Miscellaneous Internal Drug Products concluded no clinical studies were necessary to demonstrate effectiveness
- Symptom complex is complicated, including a variety of signs/symptoms of varying frequency and severity



2009 Organ-Specific Warning

- Final monograph for acetaminophen warns of hepatotoxicity, which is also associated with alcohol use



Overindulgence Tentative Final Monograph (12/24/91)

- Permits sale of antacid-analgesic for various indications, including “upset stomach with hangover”
- Permits sale of analgesic-caffeine products for “temporary relief of minor aches and pain associated with a hangover. Helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness associated with a hangover”
- Permits the sale of combination products containing acetaminophen for hangover

Summary

- The monograph has a lengthy history and resulting complex structure
- The issues of upset stomach and hangover are interwoven and touch upon four monographs
 - Internal Analgesic -- Overindulgence
 - Antacid -- Stimulant
- Given advances in our understanding of analgesics since 1991, it is time to readdress these important combinations that can be marketed under these monographs



Thank You



Analgesic Combinations in the Over-the-Counter (OTC) Monographs

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Agenda

- Over-the Counter (OTC) Monograph Process
- Antacid and Analgesics Combination Products in OTC Monographs
- Labeling for Antacid-Monograph Combination Products
- Summary



Monograph

- Regulation that specifies conditions of use under which a drug product is considered “generally recognized as safe and effective” (GRASE)
- Conditions include active ingredient, allowed concentrations, dosage forms, labeling, and other requirements
- Drugs that meet these standards can be marketed without FDA pre-review



Monograph Process

- Established in response to 1962 Harris-Kefauver amendments to the Food, Drug and Cosmetic Act
 - Requires drugs to demonstrate efficacy
 - FDA established the OTC Drug Review
 - OTC active ingredients assigned to a therapeutic category
 - Advisory Review Panels evaluated data and recommended active ingredients that they determined to be safe and effective for FDA's review

Combination Rule

- An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining....does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides a rational concurrent therapy for a significant proportion of the target population.
 - 21 CFR 330.10(a)(4)(iv)

Antacid Monograph

- April 5, 1973: Recommendations of Antacid Advisory Panel published as ANPR
 - Panel reviewed antacid ingredients (e.g. calcium carbonate, magnesium hydroxide)
 - Rational to combine an antacid with an analgesic for concurrent symptoms
- November 12, 1973: FDA published TFM
 - Comments contended antacid-aspirin combination unsafe for use in individuals with gastric complaints
 - FDA concluded that labeling would be sufficient to ensure proper use

Antacid Monograph

- June 4, 1974: FDA published Final Monograph
 - Comments questioned safety of antacid-aspirin combination products for treatment of GI symptoms
 - FDA amended monograph to limit combination products to dosage forms intended for ingestion as a solution
 - All data available were derived from studies and experience with products in solution
 - FDA noted the safety, effectiveness and appropriate labeling of analgesic component remained under review by the Internal Analgesic Panel
 - Antacid Final Monograph codified in 21 CFR, Part 331

Internal Analgesic Monograph

- July 8, 1977: Recommendations of Internal Analgesic Advisory Panel published as ANPR
 - Only acetaminophen be combined with antacid ingredients for relief of concurrent symptoms
 - Aspirin combined with antacid ingredients (regardless of antacid strength) be labeled for analgesic indications only
 - FDA acknowledged disparity between Antacid Final Monograph and the Internal Analgesic Advisory Panel's recommendations and sought comment



Internal Analgesic Monograph

- November 16, 1988: FDA published TFM
 - Aspirin and acetaminophen only GRASE ingredients for antacid-analgesic combinations
 - Rule amended to limit antacid-aspirin combination products to dosage forms intended for ingestion as a solution
 - FDA did not receive data showing the combination in solution “presents the risk of massive GI hemorrhage... in normal individuals.” (53FR, pg 46227)
 - Label warning “Do not take this product if you have stomach problems (such as heartburn, upset stomach or stomach pain) that persist or recur, or if you have ulcers or bleeding problems, unless directed by a doctor”

Antacid Indications

- Antacid Final Monograph:
 - Heartburn, sour stomach and/or acid indigestion (1973/1974)
 - Upset stomach (1979/1982)
 - Codified at 21 CFR 331.15(b)
- Upset stomach due to overindulgence in food and drink with associated symptoms of heartburn, nausea, fullness (1991), belching and gas (2005)
- Upset stomach associated with hangover (1991)



Overindulgence Monograph

- October 1, 1982: Recommendations of Advisory Review Panel on OTC Miscellaneous Internal Drug Products published as ANPR
- Reviewed drug products for the relief of symptoms due to:
 - Overindulgence in the combination of food and drink
 - Hangover

Overindulgence Monograph

- Hangover defined as “a condition consisting of a complex of symptoms involving the gastrointestinal, neurologic and metabolic systems that follows recent excessive alcohol ingestion. The symptoms may include nausea, heartburn, thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pains, headache, dullness and/or depression or irritability.”
- Panel concluded no clinical studies needed to demonstrate efficacy; logical for consumers to self-treat the wide variety of symptoms with GRASE analgesics, antacids and stimulants (caffeine)



Overindulgence Monograph

- December 24, 1991: FDA published TFM
- Added indications of overindulgence in food and drink for antacids and antacid-analgesic combinations
- Added indication of hangover relief for:
 - Antacid-analgesic combinations (GI symptoms)
 - Analgesic-stimulant (caffeine) combinations (fatigue or drowsiness symptoms)

Overindulgence Monograph

- December 24, 1991 TFM also amended Antacid, Internal Analgesic and Stimulant monographs
- Ruled out antacid/analgesic/caffeine and antacid/caffeine combinations for hangover relief
 - Antacid and caffeine is an irrational combination, as caffeine stimulates hydrochloric acid production and antacids treat symptoms associated with high levels of hydrochloric acid



Overindulgence Monograph

Indication	Drugs
<p>For the temporary relief of minor aches and pains with upset stomach due to overindulgence in food and drink (with associated symptoms of heartburn, fullness and nausea)</p> <ol style="list-style-type: none">1. Establishes the Overindulgence Monograph for overindulgence indications2. Defines upset stomach due to overindulgence in food and drink symptoms in the Overindulgence Monograph3. Amends the Antacid Monograph to include the overindulgence indication for antacids alone and in combination with analgesics4. Amends the Internal Analgesic Monograph for the overindulgence indication in combination with antacids	<p>Antacid and acetaminophen in oral dosage form</p>
	<p>Antacid and aspirin marketed in a form intended for ingestion as a solution</p>

Overindulgence Monograph

Indication	Drugs
<p>For the temporary relief of minor aches and pains with upset stomach associated with hangover</p> <ol style="list-style-type: none"> 1. Establishes the Overindulgence Monograph for hangover indications 2. Defines hangover in the Overindulgence Monograph 3. Amends the Internal Analgesic Monograph to include the hangover relief indication for analgesics in combination with antacids <p>Antacid Monograph itself is not amended to cross-reference, so this indication is only seen in the Internal Analgesics Monograph (although it applies to both)</p>	<p>Antacid and acetaminophen in oral dosage form</p> <hr/> <p>Antacid and aspirin marketed in a form intended for ingestion as a solution</p>



Overindulgence Monograph

Indication	Drugs
<p>For the temporary relief of minor aches and pains associated with a hangover. Helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness associated with a hangover</p>	<p>Caffeine and acetaminophen in oral dosage form</p>
<ol style="list-style-type: none">1. Establishes the Overindulgence Monograph for hangover indications2. Defines hangover in the Overindulgence Monograph3. Amends the Internal Analgesic Monograph to include the hangover relief indication for analgesics in combination with stimulants (caffeine)4. Amends the Stimulant Monograph to cross-reference the Internal Analgesic Monograph indication	<p>Caffeine and aspirin in oral dosage form</p>



Labeling for Antacid-Analgesic Combination Products

- Current labeling indications:
 - Temporary relief of minor aches and pains with heartburn, sour stomach, acid indigestion and upset stomach associated with these symptoms
 - Temporary relief of minor aches and pains with upset stomach associated with overindulgence in food and drink
 - Associated symptoms of heartburn, nausea, fullness, belching and gas
 - Temporary relief of minor aches and pains with upset stomach associated with hangover

Antacid-Aspirin Combination Labeling

- Revisions to aspirin labeling have sought to improve safe use of aspirin in individuals with stomach complaints:
 - December 26, 2006 TFM: introduced new stomach bleeding warning to mitigate risk with aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs)
 - Proposed as a result of September 20, 2002 NDAC meeting that reviewed data regarding GI bleeding and made labeling change recommendations



Antacid-Aspirin Combination Labeling

- April 29, 2009 Final Rule: established stomach bleeding warning and other safety labeling changes for aspirin and other NSAIDs
- Stomach bleeding warning published in 21 CFR 201.326

Antacid-Aspirin Combination Labeling

Stomach bleeding warning: This product contains an NSAID, which may cause severe bleeding. The chance is higher if you

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs [aspirin, ibuprofen, naproxen or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed



Antacid-Aspirin Combination Labeling

Ask a doctor before use if

- Stomach bleeding warning applies to you
- You have a history of stomach problems, such as heartburn



Summary

- Monograph regulations provide for OTC marketing of antacid-analgesic combination drug products for concurrent symptoms
- Antacid-aspirin combination drug products are limited to dosage forms for ingestion as a solution
- Antacid-acetaminophen combination drug products have no such limitation



Summary

- Antacid-aspirin combination products for the relief of GI symptoms has been a point of comment regarding safety throughout the rulemaking process
 - Antacid Advisory Panel and Internal Analgesics Advisory Panel reached different conclusions
- Labeling revisions have sought to improve the safe use of aspirin in individuals with a history of stomach complaints





Joint Nonprescription Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting

Postmarketing Safety Data

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April 4, 2017



Outline

- Drug Utilization
 - Quintiles IMS, National Sales Perspective
 - OTC sales of combination effervescent products
- Postmarketing
 - FDA Adverse Event Reporting System (FAERS)
 - Major bleeding events
- Epidemiology
 - Review of published literature
- Summary

Drug Utilization Data

Quintiles IMS, National Sales Perspectives



Effervescent Combinations

- FDA specified that aspirin/antacid combinations approved for GI upset/hangover should be marketed in solution. In practice, this means they are effervescent.
- “Effervescent” refers to combinations that include sodium bicarbonate in combination with citric acid.
- Drug use analyses used the term “effervescent” for both aspirin and acetaminophen combinations.
- Literature searches were performed both with and without the term “effervescent”.



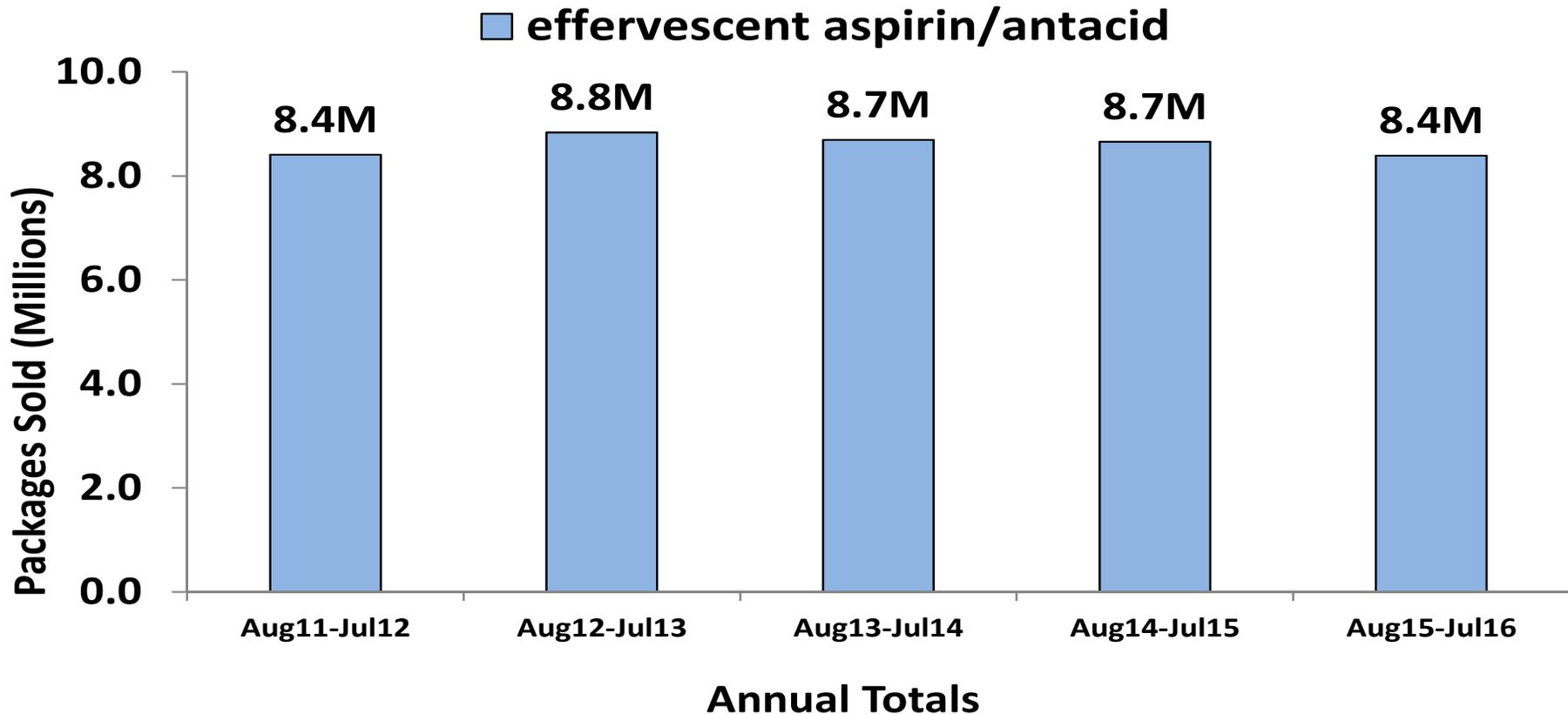
Drug Utilization Data

- **Sales Database:**
 - OTC product sales from manufacturers to U.S. retail pharmacies
 - Quintiles IMS, National Sales Perspectives
- **Active Ingredients:**
 - Combination effervescent aspirin/antacids
 - Combination effervescent acetaminophen/antacids
 - Combination analgesic*/caffeine

* Analgesic products containing aspirin or acetaminophen

OTC Sales Data

Nationally estimated number of packages¹ sold for effervescent aspirin/antacid products from manufacturers to U.S. retail channels of distribution, August 2011-July 2016



Source: Quintiles IMS, National Sales Perspectives™. Aug 2011 - July 2016. Extracted November 2016.



Limitations of OTC Data

- No direct to consumer sales were available
- IMS Health estimates approximately 50% capture of the total OTC market
- OTC sales do not include data from internet sales, convenience stores, specialty stores, or vending machines
- Data captured by active ingredient only; data on indication for use were not available

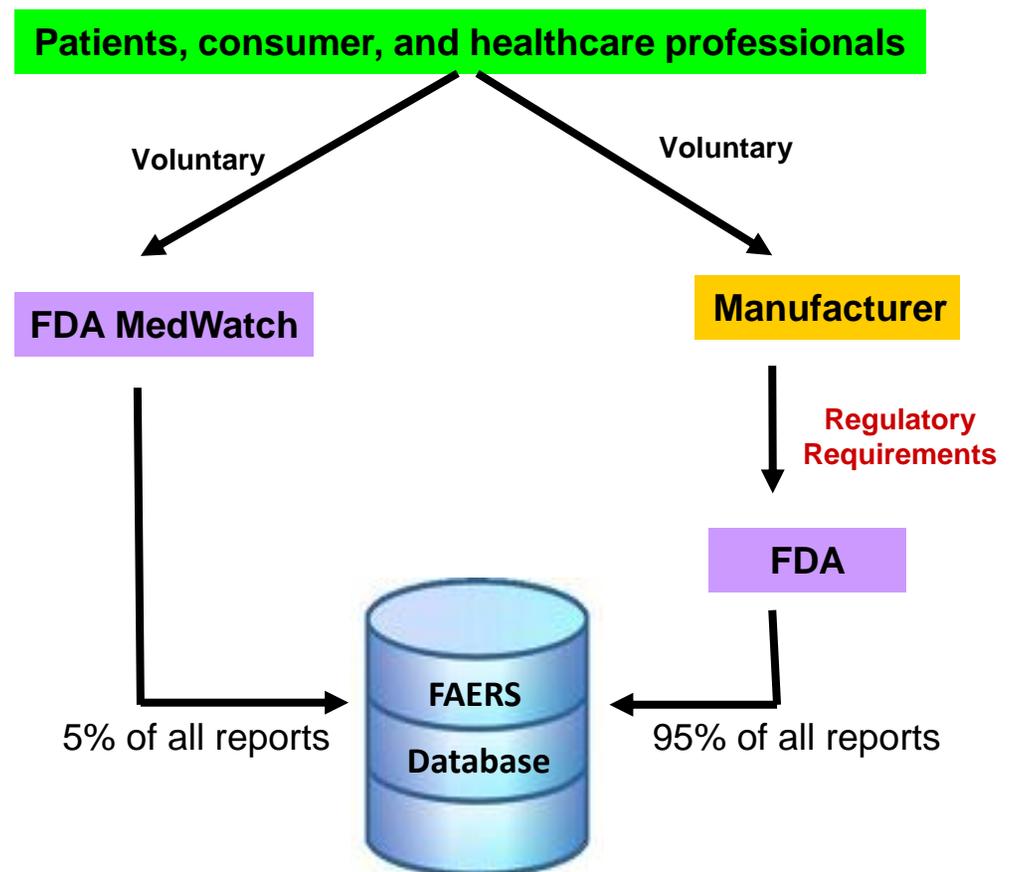
FDA Adverse Event Reporting System (FAERS)





FDA Adverse Event Reporting System (FAERS)

- Computer database of spontaneous reports for human drugs and biologics
 - Mandatory reporting by manufacturers
 - Voluntary reporting by healthcare professionals, patients, and the general public
- > 13 million reports since 1969
 - Over 1.6 million new reports in 2016





FAERS Strengths

- Computerized database
- Includes all U.S. marketed products
- Includes all uses (both approved and off-label use)
- Includes broad patient populations:
 - elderly, children, pregnant women, co-morbidities
- Simple, relatively inexpensive reporting system
- Useful for events that occur shortly after exposure
- Detection of events not seen in clinical trials (“signal generation”)
- Detection of events with rare background rate
- Identification of possible risk factors, populations, and other clinically significant emerging safety concerns



Limitations of FAERS

- Quality of report is variable
 - information is limited in some reports
- Under-reporting –not every adverse event is reported (passive surveillance)
- Difficult to attribute events with high background rates or long latency periods to the product
- Causal relationship between a product and an event is not required for reporting to the FDA
- Reporting biases
- FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population [the actual number of events in the population (numerator) and the number of exposed patients in the population (denominator) are not known]

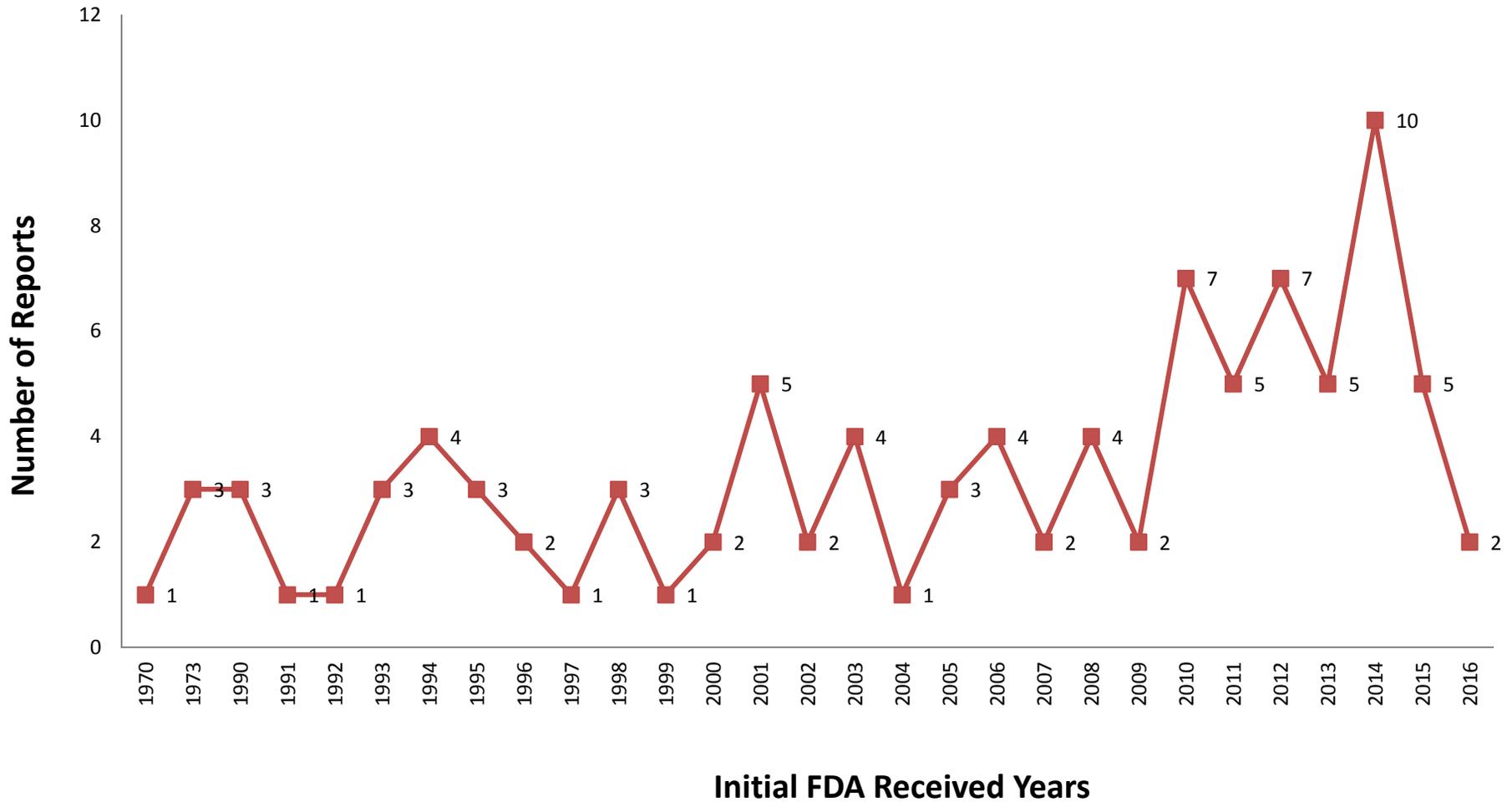
Primary Objectives of FAERS Analyses

- To identify **major bleeding events** associated with the aspirin or salicylate component of OTC analgesic combination products indicated for hangover or overindulgence
- To identify **liver toxicity events** associated with the acetaminophen component of OTC analgesic combination products indicated for hangover or overindulgence
 - We did not investigate liver injury associated with effervescent acetaminophen/antacid products further because there are no currently marketed effervescent acetaminophen/antacid products available on the US market.

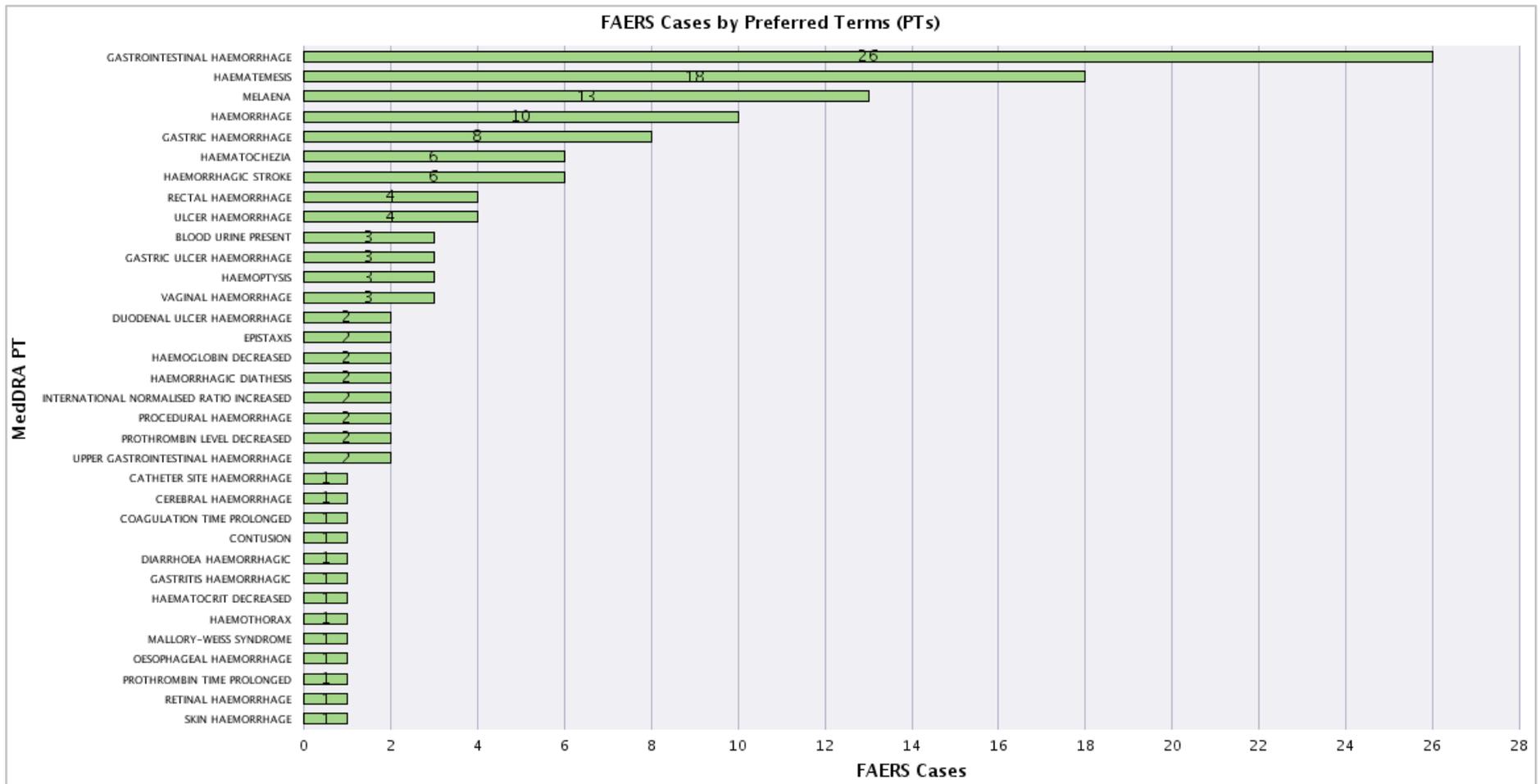
Reporting Trend for Aspirin/Antacid FAERS Reports for All Bleeding Events (n=96)



Total Reports by Initial FDA Received Years



Preferred Terms for All Aspirin/Antacid FAERS Reports Associated with SMQ Haemorrhage, Including Non-Major Bleeding Events (n=96)





FAERS Case Definition for Major Bleeding Events

The FAERS database was searched to identify serious adverse events related to major bleeding associated with effervescent aspirin/antacid and analgesic/caffeine combination products indicated for overindulgence/hangover.

Cases Inclusions:

- Cases reporting major bleeding events resulting in hospitalization or blood transfusion

AND

- Events having temporal association with OTC combination products with aspirin or salicylate marketed for overindulgence/hangover



FAERS Case Definition for Major Bleeding Events –cont.

Case Exclusions:

- Case where bleeding event did not result in hospitalization or blood transfusion
- Case did not report a bleeding event
- Case contained insufficient information to determine the severity of the bleed or to determine a temporal association with the product
- Product reportedly used in the narrative did not contain aspirin or salicylate



FAERS Search Results

- Combination products containing analgesic/caffeine for an indication of hangover or overindulgence
 - No cases of major or non-major bleeding events identified
- Major bleeding events involving effervescent aspirin/antacid products
 - 20 cases identified between January 1, 1969, to July 31, 2016

Potential Reasons for Limited FAERS Cases

- Possible miscoding of products
- Underreporting for older drug products with widely known adverse events (e.g. aspirin and gastrointestinal bleeding)
- Years on the market (Weber effect)
- No requirement for manufacturers to report serious adverse events associated with OTC drugs to the FDA until the recent amendment to the Federal Food, Drug, and Cosmetic Act in December 2006 (Public Law 109-462)
- Paucity of information in individual reports to adequately meet a case definition



Trends in Year of Receipt for FAERS Cases of Major Bleeding through July 31, 2016 (n=20)

Year	Number of Cases
1970	1
1973	2
1996	1
2000	1
2002	1
2003	1
2004	1
2005	1
2006	1
2007	1
2008	1
2010	3
2011	2
2013	1
2014	2

Major Bleeding Event Characteristics with Use of Effervescent Aspirin/Antacid Products, received by FDA through July 31, 2016 (n=20)

Age (n=16)	Mean	61
	Median	67
	Range	24 to 91
Sex	Male	6
	Female	13
	Unknown	1
Country of Reporter	United States	18
	Foreign	2
Reporter	Healthcare Professional	9
	Consumer	1
	Other	3
	Not reported	7
Serious Outcomes	Death	1
	Hospitalized	16
	Other serious	8

Major Bleeding Event Characteristics with Use of Effervescent Aspirin/Antacid Products, received by FDA through July 31, 2016 (n=20)

Reason for Use	Gastrointestinal issues	8
	Cold/infection	2
	Pain (headache)	1
	Hayfever	1
	Unknown	8
Co-suspect medications in addition to effervescent aspirin/antacid (n=12)	Aspirin	8
	Ibuprofen	4
	Naproxen	2
	Clopidogrel	1
	Indomethacin	1
	Prednisone	1
	Warfarin	1
Location of major bleeding event	Upper GI Bleed	10
	Lower GI Bleed	3
	Unspecified	7
Transfusion required?	Yes	9
	No	6
	Not reported	5



Fatal Bleeding Event Case

- Domestic case from 1970 of a **69-year-old** female patient who developed a **“massive” GI bleed** and was **hospitalized**
- Patient had been using **aspirin & effervescent aspirin/antacid** (both medications with unknown dose, frequency, duration of use, and indication)
- Her **initial hemoglobin was 8** (no units or normal range reported) which **decreased to 5.3**
- The patient received **multiple blood transfusions (“14 units”)** & was treated with an ice water irrigation of her stomach
- The patient **died on the fifth day** of her hospitalization
- No cause of death was provided & no autopsy was performed
- No medical history was provided.



FAERS Findings

- At least one risk factor for developing stomach bleed was reported in 80% (16/20) of patients which included:
 - Age > 60 years (n=12)
 - Concomitant use of antithrombotics, NSAIDs, and/or prednisone (n=12)
 - History of stomach ulcers (n=1)
 - History of alcohol abuse (n=1)
- 40% (8/20) of cases reported using effervescent aspirin/antacid products for a GI issue (e.g., heartburn, indigestion, GI pain)



Review of Published Literature

- Population-based observational studies
 - No relevant studies of analgesic/antacid or analgesic/caffeine combination products
- Randomized Controlled Clinical Trials (RCTs)
 - 14 RCTs for aspirin/antacid, acetaminophen/antacid, or aspirin/caffeine products
 - Important limitations, including short follow-up (cannot assess long-term effects)
 - One noteworthy crossover RCT comparing aspirin/acetaminophen/caffeine vs. aspirin/antacid products (Dammann 2004)
 - New gastric mucosal erosions and bleeding observed more often in healthy subjects taking aspirin/caffeine vs. aspirin/antacid combinations

Summary

- Total sales of effervescent aspirin/antacid products captured in the IMS Database ranged from 8.4 to 8.8 million packages sold annually from August 1, 2011, through July 31, 2016
- There were no sales of effervescent acetaminophen/antacid products captured during the review period
- 20 FAERS cases of major bleeding events and effervescent aspirin/antacid products noted for the time period from January 1, 1969, through July 31, 2016
 - We acknowledge there are few FAERS reports documenting major bleeding over many years of marketing, however given the known gastrointestinal toxicity of aspirin, a dearth of FAERS data should not be interpreted as a lack of risk for gastrointestinal bleeding
- Published population-based studies and RCTs largely uninformative
 - One noteworthy RCT suggested gastric risks from aspirin/caffeine combination products.



Acknowledgments

- Michael D. Blum MD, MPH
- Elisa Braver, PhD
- Allen Brinker, MD
- Grace Chai, LCDR, PharmD
- Patty Greene, PharmD
- S. Christopher Jones, PharmD, MS, MPH
- Lynda McCulley, PharmD, BCPS
- Simone Pinheiro, ScD
- Travis Ready, PharmD
- Lockwood Taylor, PhD
- Margee Webster, PharmD, BCPS



Selected Clinical Literature Overview

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Clinical Literature Search

- PubMed, EMBASE, and Google search produced over 250 articles
- Articles providing clinical safety information were included in review
- Focus was on combination products intended to treat gastrointestinal (GI) and hangover symptoms, and not on single active ingredient products
- Although number of articles was large, actual data are somewhat sparse



Clinical Concerns

- Aspirin-containing combination products used to treat gastrointestinal (GI) symptoms
- Acetaminophen-containing combination products used to treat symptoms of hangover



Do aspirin-containing combination products used for the treatment of gastrointestinal symptoms have a negative impact on the gastrointestinal tract?

Aspirin Basics

- Over-the-counter (OTC) Indications: For relief of headache, minor aches and pains, menstrual pain, and toothache; and for reduction of fever from colds and flu
- OTC Dose: 325 mg to 4000 mg per day
- Nonselective cyclo-oxygenase (COX) inhibitor
- Analgesic and antipyretic effects via dose-dependent decrease in prostaglandin E₂ synthesis (via COX inhibition)
- Decreased prostaglandin synthesis also reduces multiple prostaglandin-mediated gastric mucosal protective mechanisms
- Decreased platelet aggregation via irreversible inhibition of thromboxane A₂ production (via COX inhibition)
- Relevant adverse events (AEs): Abdominal pain, nausea, vomiting, heartburn, gastritis, and GI bleeding
- Upper GI bleeding = most frequent bleeding complication

Development of Stomach Bleeding Warning

- Nonprescription Drugs Advisory Committee (NDAC) meeting in September 2002 discussed possible Stomach Bleeding Warnings. Unanimously agreed that the evidence of bleeding risk associated with OTC nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, supported a Stomach Bleeding Warning on the Drug Facts label (DFL)
- Proposed Rule published December 2006
- Final Rule with Organ Specific Warnings published in Federal Register on April 29, 2009 (21 CFR 201.326); required Stomach Bleeding Warnings on DFL of all NSAIDs, including aspirin



- **Drug Facts Label Stomach Bleeding Warning:**
This product contains an NSAID, which may cause severe bleeding. The chance is higher if you:
 - are age 60 or older
 - have had stomach ulcers or bleeding problems
 - take a blood thinning (anticoagulant) or steroid drug
 - take other drugs containing prescription or nonprescription NSAIDs
 - have 3 or more alcoholic drinks every day while using this product
 - take more or for a longer time than directed
- “Ask a doctor before use if” section revised to include:
 - Stomach bleeding warning applies to you
 - You have a history of stomach problems, such as heartburn
- Despite these warnings, FDA continues to receive case reports of GI bleeding associated with use of aspirin-antacid combination products

Do aspirin-containing combination products have a safer GI profile compared to aspirin alone?

- An article¹ raised concerns regarding claims that, unlike plain aspirin, aspirin-sodium bicarbonate-citric acid combination products did not cause gastric irritation
- Article expressed concern regarding using aspirin-antacid combination products to treat GI symptoms
- Aspirin may cause gastritis and aggravate peptic ulcers
- Noted that aspirin-antacid combination products have been associated with hematemesis and melena when administered after heavy alcohol intake

¹ The Medical Letter 1973

Aspirin-Antacid Combination Products May Cause Bleeding if Used for Dyspepsia

- Series of 10 patients who were admitted to a UK Hospital over 6 years after taking aspirin-antacid products for upset stomach or dyspepsia²
- 7 of 10 patients required blood transfusions
- 2 of 10 required emergent surgery
- Majority of the bleeding due to erosions or ulcers

Worldwide Regulatory Actions for OTC Aspirin-Antacid Combination Products with GI Indications

- 2004: Spain withdrew aspirin component from OTC combination aspirin-antacid product and allows only the antacid component to market for GI indications⁴
- 2005: France removed GI indications from OTC aspirin-antacid product
- 2010: United Kingdom removed GI indications from OTC aspirin-antacid products
- Published literature from 2009: 32 out of 68 countries where OTC aspirin-antacid combination products are allowed to market, do not allow GI indications⁴

⁴ de Abajo et al 2009

Aspirin in Hangover Combination Drug Products

- Hangover associated with multiple GI symptoms
- Some combination products for hangover include aspirin
- Similar to the concern for aspirin-antacid combination products for GI uses, there is concern for potential adverse GI effects of aspirin-containing combination products (e.g. aspirin-caffeine combinations) for hangover

Summary Points Regarding OTC Aspirin-Antacid Combination Products for GI Indications

- Relationship between aspirin-antacid combination products and GI bleeding remains a persistent concern at FDA, although data are sparse
- 2002 NDAC Committee voted unanimously to add Stomach Bleeding Warnings on the Drug Facts label (DFL)
- Final Rule in April 2009 required that DFL of all NSAIDs, including aspirin, must add Stomach Bleeding Warnings
- FDA continues to receive case reports of major GI bleeding events



Acetaminophen-Containing Combination Products Used to Treat Symptoms of Hangover



Effects of Alcohol

- Standard drink in the U.S.: 14 g of alcohol
- Binge Drinking: Pattern of alcohol drinking that leads to blood alcohol concentration of 0.08 g/dL⁵
- Virtually all chronic users will develop fatty liver but only minority progress to further stages of alcoholic liver disease (two most important risk factors: amount and duration)⁶
- Metabolism: Primarily in the liver⁶
- Alcohol and its metabolites primarily affect the liver, but alcohol may cause esophageal and gastric inflammation⁷
- Alcohol a leading cause of liver failure

⁵ NIAAA

⁶ Liu 2014

⁷ Rocco et al 2014

Acetaminophen Basics

- Indications: For temporary relief of minor aches/pains (headache, muscle aches, backache, arthritis, the common cold, menstrual cramps, toothache), and to reduce fever
- OTC Dose: 325 mg to 4000 mg per day
- Relevant adverse events: nausea, vomiting
- Severe but less common adverse event: hepatotoxicity
- Under normal circumstances, acetaminophen is metabolized via multiple pathways but one pathway leads to development of N-acetyl-p-benzoquinone imine (NAPQI) which is a liver-toxic substance
- Fasting and malnutrition may be risk factors for hepatotoxicity due to reduced glutathione stores (NAPQI rapidly conjugates with glutathione forming nontoxic cysteine and mercaptate compounds)



Acetaminophen Basics (cont.)

- Leading cause of drug-induced liver failure
- About 50% of drug-induced liver failure cases may be associated with acetaminophen⁸
- 50-66% of acetaminophen overdoses are unintentional
- Consumers often fail to recognize the consequences of exceeding maximum dose⁹

⁸ Larson et al 2005

⁹ King et al 2011

Does acetaminophen have a subclinical effect on the liver?

- Single-blind (subjects blinded), placebo-controlled, 5-treatment, longitudinal study of 145 healthy adults in two inpatient clinical pharmacology research facilities
- Subjects administered 4 g/day of acetaminophen; 1 of 3 acetaminophen-opioid combinations with 4g/day acetaminophen component; or placebo. All treatments administered for two weeks
- Serum alanine aminotransferase (ALT) elevated (3x upper limit of normal (ULN)) in 39% of subjects receiving acetaminophen¹⁰
- 23% of subjects treated with acetaminophen had ALT >5x ULN
- Percentage of subjects with ALT >3x ULN or >5x ULN was similar across acetaminophen groups
- No subject had trough acetaminophen above therapeutic range
- No subjects who received placebo developed ALT >3x ULN
- All subjects were asymptomatic



Does acetaminophen in combination with recent alcohol use increase the risk of hepatotoxicity compared to use of either alone?

Chronic Moderate to Heavy Alcohol Use May Potentiate the Toxic Effects of Acetaminophen

Cases of acute liver failure (ALF) have been reported in moderate alcohol users who ingest as little as 4 g of acetaminophen in 24 hours¹¹

¹¹ Draganov et al 2000

Alcohol May be a Cofactor in Lower-Dose Users of Acetaminophen who Develop Acute Liver Failure

- 662 hospitalized cases of ALF
- For 302 cases, medical record identified acetaminophen as cause of ALF. Authors reviewed all cases and eliminated some due to lack of data or competing etiologies. Identified 275 cases (42%) for an acetaminophen ALF study group.
- 19 of 275 acetaminophen users with ALF took ≤ 4 g/day of acetaminophen (65% of these cases met criteria for alcohol abuse). By comparison, 37% of those who took >4 g/day of acetaminophen met criteria for alcohol abuse. Alcohol abuse criteria: >40 g/day in males and >20 g/day in females
- 22% of the total patients used 2 or more preparations of acetaminophen
- Authors concluded that alcohol may be a cofactor in the patients who developed ALF after doses of acetaminophen ≤ 4 g/day

Effect of Acetaminophen on Hepatic Tests of Alcohol Detoxification Patients

- Prospective double-blind, randomized, placebo-controlled trial involving 443 adult alcoholic patients admitted to two alcohol detoxification centers
- Patients were randomized to acetaminophen 4 g/day or placebo for 3 consecutive days (patients excluded if aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 200 IU at baseline)
- Total of 308 received acetaminophen and 135 patients received placebo
- Mean baseline ALT no different between acetaminophen and placebo groups
- Mean peak ALT (primary endpoint) no different between acetaminophen and placebo groups
- Post-hoc analyses: Total of 32 patients (24 or 8% of acetaminophen group, 8 or 6% of placebo) developed ALT >3x ULN, and total of 11 patients developed ALT >200 IU/L (9 or 3% of acetaminophen, 2 or 1% of placebo), at some time during the study
- Post-hoc analyses had limited power

Are analgesic-caffeine combination products a rational combination for treatment of a hangover?

- Combination analgesic-caffeine products are marketed for relief of hangover symptoms
- Caffeine stimulates gastric acid secretion and reduces competence of lower esophageal sphincter
- Caffeine may exacerbate GI symptoms of hangover, and may potentiate adverse GI effects of aspirin and of alcohol



Summary

- FDA continues to receive case reports of major GI bleeding events associated with use of aspirin-antacid combination products for GI uses; bleeding appears to be due to aspirin component
- Unclear if aspirin-antacid combination products are rational combinations for treatment of GI symptoms



Summary (cont.)

- Unclear if combination products containing acetaminophen or aspirin are rational combinations for treatment of hangover
- Acetaminophen is a leading cause of drug-induced liver failure in the U.S.
- Moderate alcohol consumption may be associated with higher risk of acetaminophen-related liver AEs
- Consumers who use acetaminophen-containing combination products in the setting of recent excessive alcohol use may increase their risk of liver injury



Summary (cont.)

- Caffeine stimulates gastric acid secretion and reduces competence of the lower esophageal sphincter
- Consuming caffeine-aspirin combination products in the setting of recent excessive alcohol intake may increase the incidence of gastric adverse events



Acknowledgments

- Steven Adah, PhD
- CAPT Janice Adams-King, MSN, MS, CRNP, CPHN (USPHS)
- Francis Becker, MD
- FDA Library Staff
- Lesley-Anne Furlong, MD
- Charles Ganley, MD
- Lori Griner, PhD
- Kevin Lorick, PhD
- Karen Mahoney, MD
- Theresa Michele, MD
- Valerie Pratt, MD
- CAPT (USPHS Ret) Mary Vienna, RN, MHA

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Joint Meeting of the Nonprescription Drugs Advisory Committee
and the Drug Safety and Risk Management Advisory Committee
for OTC Analgesic Combination Products for Upset Stomach or Hangover

CHARGE TO THE COMMITTEE

Valerie Pratt, MD
Deputy Director for Safety
Division of Nonprescription Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
April 4, 2017

Antacid – Aspirin Key Points

- Antacid-analgesic products marketed for upset stomach and hangover indications
- Antacid-aspirin use for GI symptoms has been a point of comment throughout rulemaking
- Aspirin is associated with bleeding risk
- 21 CFR 330.10(a)(4)(iv) requires that OTC drug combinations provide rational concurrent therapy
- Concern persists for antacid-aspirin products
- Drug Safety Communication released June 2016

Monograph Key Points

- December 24, 1991 TFMs were part of a larger effort to establish a separate monograph for Overindulgence
- As a result, “upset stomach” and “hangover” are interwoven and touch upon four monographs
 - Internal Analgesic
 - Overindulgence
 - Antacid
 - Stimulant

Hangover Key Points

- Advisory Review Panel concluded no clinical studies were necessary to demonstrate effectiveness
- 2009 Organ-Specific Warnings final monograph for acetaminophen warns of hepatotoxicity, which is also associated with alcohol use
- Monograph permits the sale of combination products containing acetaminophen for hangover



Question 1

DISCUSS: Discuss the safety of the use of OTC analgesic combination products for the relief of minor aches and pains associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea.



Question 2

VOTE: Is the combination of an analgesic with antacids a rational combination for over-the-counter (OTC) use for the relief of minor aches and pains associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea?



Question 3

Hangover is defined in the monograph as a condition consisting of a complex of symptoms involving the gastrointestinal, neurologic, and metabolic system that follows recent acute and excessive alcohol ingestion. The monograph states that the symptoms may include nausea, heartburn, thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability.



Question 3 (cont.)

DISCUSS: Discuss whether or not the treatment of hangover is an appropriate indication for OTC drug products. If the hangover indication is appropriate, which ingredients would be options for the treatment of the symptoms?

We are particularly interested in a discussion of aspirin or acetaminophen as acceptable ingredients to include in combination products for the treatment of hangover. Consider in your discussion the indications for hangover in the monograph, the association of alcohol and NSAIDs with gastrointestinal bleeding, the association of alcohol and acetaminophen with liver toxicity, and the safety information presented in this meeting.



THANK YOU

