Empower self-care by preserving and expanding choice and availability of consumer healthcare products

serving the self-medication industry since 1881
Advisory Committee Charges

1. Safety of OTC analgesic combination products for relief of minor aches and pains associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas or nausea.

2. Vote: analgesic + antacid as rational combination for symptoms above

3. Hangover indication for OTC drug products
Alka-Seltzer® Aspirin/Antacid Combination Products

Presentation to the
Nonprescription Drugs Advisory Committee
Drug Safety and Risk Management Advisory Committee
Joint Meeting
April 4, 2017

Alka-Seltzer® Aspirin/Antacid Combination Products

Andre Schmidt, MD, PhD
Medical Affairs US
Bayer HealthCare LLC
Bayer’s Position

- Benefit-risk profile for Alka-Seltzer® Aspirin (ASA)/antacid combination products remains favorable when used as labeled

- In recent years Bayer has focused its US consumer innovation on Alka-Seltzer® products for relief of occasional heartburn and upset stomach

- Given this focus and to reduce or eliminate any potential for consumer misuse, Bayer has made the decision to reformulate all Alka-Seltzer® ASA/antacid combination products by removing the ASA component and the analgesic indication.

Alka-Seltzer® Effervescent Products

- Alka-Seltzer® effervescent tablets were introduced in the 1930’s
  - Millions of use experiences per year worldwide

- Three formulations of Alka-Seltzer® in the United States contain ASA/antacid combination
  - Alka-Seltzer® Original, Lemon Lime, Extra Strength
  - From 2010-2016, ~1.4 billion doses sold
Alka-Seltzer® ASA/Antacid Product Formulations

United States Alka-Seltzer® ASA/antacid combination formulations

<table>
<thead>
<tr>
<th>Active Ingredients in each tablet</th>
<th>Alka-Seltzer® Original</th>
<th>Alka-Seltzer® Lemon Lime</th>
<th>Alka-Seltzer® Extra Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>325 mg</td>
<td>325 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>Anhydrous Citric acid</td>
<td>1,000 mg</td>
<td>1,000 mg</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>1,916 mg</td>
<td>1,700 mg</td>
<td>1,985 mg</td>
</tr>
</tbody>
</table>

Directions*

2 tablets every 4 hours
2 tablets every 6 hours

*Adults and children 12 years and over
Maximum duration of use 10 days

Alka-Seltzer® ASA/Antacid Products Conform to Applicable Monographs

- FDA Over-The-Counter (OTC) Drug Monograph process established for drugs marketed in the United States before May 11, 1972

- Active ingredient-based regulations that identify acceptable ingredients, uses and labeling for each OTC drug class

- Monographs dictate indications and warnings
Alka-Seltzer® ASA/Antacid Product Uses for the Temporary Relief of:

- Heartburn, acid indigestion, and sour stomach when accompanied with headache or body aches and pains

- Upset stomach with headache from overindulgence in food or drink

- Headache, body aches, and pain alone

Alka-Seltzer® ASA/Antacid Products Carry Monograph Required Warnings, Including Risk of Stomach Bleeding

- FDA issued final rule (2009) requiring a stomach bleeding warning for OTC Internal Analgesic NSAID containing drug products as follows:

  Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach 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
Alka-Seltzer® ASA/Antacid Combination
Products Rationale

ASA
Pain reducer

+ Antacid
Neutralize Stomach Acid

- Efficacious and rapid action in relieving combined symptoms of headache/body pain with GI symptoms caused by gastric acid

- Fixed dose combination of an antacid with a safe and effective analgesic helps to ensure appropriate dosing

Ingredient Effectiveness – Antacid
Sodium Bicarbonate & Citric Acid

- Monograph recognized pH buffering agent combination
- Demonstrated efficacy in the treatment of gastric hyperacidity
- Fast relief by increasing intra-esophageal and intra-gastric pH:

\[
\text{C}_6\text{H}_8\text{O}_7\text{(aq)} + 3 \text{NaHCO}_3\text{(aq)} \rightarrow 3 \text{H}_2\text{O}\text{ (liquid)} + 3 \text{CO}_2\text{(gas)} + \text{Na}_3\text{C}_6\text{H}_5\text{O}_7\text{(aq)}
\]

- sodium citrate    citric acid    water    carbon dioxide    sodium citrate

\[
\text{Na}_3\text{C}_6\text{H}_5\text{O}_7\text{(aq)} + 3 \text{HCl}\text{(aq)} \rightarrow \text{C}_6\text{H}_8\text{O}_7\text{(aq)} + 3 \text{NaCl}\text{(aq)}
\]

- sodium citrate    stomach acid    citric acid    sodium chloride
Effervescent Bicarbonate Solution Quickly and Significantly Increases Intragastric pH

Plot of mean intragastric pH/5 min during the entire recording period


(Acetyl)Salicylic Acid

History

- **1500 b.c.** Used as pain reliever by Egyptians and Sumerians (willow bark)
- **1876** First clinical trial published in Lancet
- **1897** Felix Hofmann (Bayer) finds adding an acetyl group reduces its irritant properties
- **1971** John Vane describes aspirin’s mechanism of action

**1974 - today**

Multiple randomized clinical trials demonstrated benefits of aspirin use in the prevention of major cardiovascular events (stroke, heart attacks)

Epidemiological research and meta-analyses indicate benefits of aspirin in prevention of colorectal cancer

Aspirin continues to be one of the most researched drugs in the world with an estimated 700 to 1,000 publications each year
ASA Exerts Its Effects Through COX Inhibition

ASA Efficacy Demonstrated Dose Response

Acute analgesic effect in patients with non-migraine headache (Von Graffenried, 1980)

Relief of moderate to severe post surgical pain (Derry, 2012)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Studies / N</th>
<th>Aspirin (%)</th>
<th>Placebo (%)</th>
<th>Relative benefit (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>2 / 213</td>
<td>33</td>
<td>26</td>
<td>1.3 (0.82 to 2.0)</td>
</tr>
<tr>
<td>600/650</td>
<td>60 / 4630</td>
<td>39</td>
<td>15</td>
<td>2.5 (2.2 to 2.7)</td>
</tr>
<tr>
<td>900/1000</td>
<td>6 / 618</td>
<td>41</td>
<td>14</td>
<td>2.7 (2.0 to 3.7)</td>
</tr>
</tbody>
</table>


Derry S, Moore RA. Cochrane Database Syst. Rev 2012 Apr 18; (4)
ASA Safety Profile is Well Characterized

- Well tolerated
- Adverse Events (AEs) are typically dose and duration dependent
- Similar safety profiles of ASA and non-ASA analgesics
  - When used according to the label at single and multiple OTC doses (Lanas, 2011)
- Serious AEs are rare with short-term use at OTC doses
  - ASA and other drugs commonly used for pain, colds, and fever (Baron, 2013; Lanas, 2011)

Gastrointestinal (GI) Risk of ASA Extensively Studied

- Inhibitory COX-1 effect on prostaglandins and GI protection is well described
- Direct irritant effect on GI mucosa can contribute to risk
- Dose and duration dependent
- Associated with underlying risk factors
GI Safety of ASA Confirmed in Meta-Analysis of Short-Term Analgesic Studies (Lanas, 2011)

- 67 Bayer sponsored RCTs; all with individual patient data available
  - 325 – 1000 mg single dose
  - Up to 4000 mg daily dose, up to 10 days
  - 82% single dose (ASA)
    - Reflects typical OTC ASA use in the general population
- Increased dyspepsia with ASA vs placebo
- GI bleeding
  - ASA = 1/6181 (effervescent ASA 0/2298)
  - Placebo = 3/3515

Lanas A, McCarthy D, Voelker M, Brueckner A, Senn S, Baron JA. Drugs R D. 2011

Literature Meta-Analysis Supports GI Safety of Short-Term ASA Use (Baron, 2013)

- Meta-analysis of short-term analgesic doses studies comparing side effects of ASA versus placebo or an active comparator
  - 325 – 1000 mg single dose
  - Up to 4000 mg daily dose, up to 10 days
  - 43% single dose (ASA)
- In short-term use, ASA was associated with a higher frequency of minor GI complaints
- No GI bleeding was reported
  - ASA = 0/6712
  - Placebo = 0/3385

Conclusions from Short-term ASA RCTs

- Minor GI complaints such as dyspepsia are modestly increased with ASA vs placebo
- GI bleeding is very rare with short-term ASA use

Bayer Pharmacovigilance
ASA/Antacid Combination Products

- Bayer has robust processes and procedures in place to collect and evaluate post marketing data
- We continually monitor for any new safety information regarding the benefit-risk profile of all products
Consider Background GI Bleeding Rates in Overall US Population

Incidence of hospitalization for UGIB/year

<table>
<thead>
<tr>
<th></th>
<th>Incidence (100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laine 2012</td>
<td>61</td>
</tr>
<tr>
<td>Peery 2015</td>
<td>58</td>
</tr>
</tbody>
</table>


Definition of Serious Adverse Event

- Any untoward medical occurrence that at any dose:
  - Results in death
  - Life threatening
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability or incapacity
  - Medically significant/important

- In addition, Bayer considers certain Preferred Terms to be automatically Serious.
Summary of Spontaneous US AE Reports for ASA/Antacid Combination Products 1982 - 2016

5042 Total Reports

516 Serious Reports

60 GI Bleeding Reports

20 Hospitalized

Reporting Rate of GI Bleeding is Consistently Low Before and After the Implementation of the Revised GI Bleeding Warnings

Bayer US spontaneous reports of GI bleeding for ASA/antacid combination products

<table>
<thead>
<tr>
<th>Reports/year of Serious GI Bleeding*</th>
<th>Jan 1, 1999** to Dec 31, 2009</th>
<th>Jan1, 2010 to Dec 31, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2</td>
<td>3.6</td>
<td></td>
</tr>
</tbody>
</table>

* Reports with a serious event in the Standard MedDRA Query GI hemorrhage
** 1999 was the first year with a serious event of GI bleeding reported in the database

The reporting rate for serious GI bleeding was estimated at 1 event / 2.4 million patients exposed (based upon product sales)
Bayer US Spontaneous Reports: Serious Adverse Events (SAEs) of GI Bleeding Have Remained Consistently Low

Most Consumers Reporting SAEs with GI Bleeding Events to Bayer Had Underlying Risk Factors Cited in the Monograph Labeling

<table>
<thead>
<tr>
<th>Age</th>
<th>Not reported</th>
<th>&gt;= 60 years</th>
<th>&lt; 60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 spontaneous reports of hospitalization in Bayer database 2010-2016*</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>25 Spontaneous reports in Bayer database 2010-2016 (serious event in SMQ** with or without hospitalization)</td>
<td>7</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant medication</th>
<th>Aspirin or NSAID</th>
<th>Anticoagulant/antiplatelet</th>
<th>No NSAID/anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 spontaneous reports of hospitalization in Bayer database 2010-2016*</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>25 Spontaneous reports in Bayer database 2010-2016 (serious event in SMQ** with or without hospitalization)</td>
<td>6</td>
<td>0</td>
<td>19</td>
</tr>
</tbody>
</table>

*5 of these reports were also highlighted by FDA in their communication of June 2016
** SMQ=Standardized MedDRA Query
**Bayer Pharmacovigilance Findings**

- Rate of spontaneous reports of SAEs with GI bleeding is low and has been consistent over time.
- Among the few consumers who reported a serious GI bleeding event many had labeled independent risk factors.
- PV data support no change to the benefit-risk profile of these products.

**Bayer’s Position**

- Benefit-risk profile for Aspirin(ASA)/antacid combination products remains favorable when used as labeled.
- In recent years Bayer has focused its US consumer innovation on products for relief of occasional heartburn and upset stomach.
- Given this focus and to reduce or eliminate any potential for consumer misuse, Bayer has made the decision to reformulate all ASA/antacid combination products by removing the ASA component and the analgesic indication.
Lanas et al. Drugs R D 2011

Methods

• Individual patient data
  – Source: Clinical Study Reports and Case Report Forms
• Bayer sponsored randomized controlled clinical trials
  – 67 studies (Phase I-IV (efficacy or pharmacokinetic) conducted between 1987 and 2008
• Aspirin dose: 325 – 1000 mg per dose and max 3000 mg per day
• Physicians-adjudicated patient-reported adverse events
• Collected per MedDRA SOC (e.g. GI disorders) and Prefered Terms (e.g. dyspesia)
• Advisory Board combined MedDRA Preferred Terms based on their clinical experience and
aggregated incidences were calculated
  – Minor dyspepsia: dyspepsia, abdominal discomfort, abdominal pain upper, epigastric discomfort, eructation, flatusulence, gastric dilatation, gastric disorders, hyperchlorhydria, nausea, stomach discomfort
  – Minor GI disorders: heartburn, nausea, vomiting and abdominal pain
• Adverse events were presented descriptively
  – Incidences / odds ratios (95% CI) / risk differences (95% CI)
• Comparison to placebo and other analgesics (ibuprofen, acetaminophen)
Baron et al. Drugs R D 2013

Methods

- Population data
  - Source: Publications
- Randomized controlled clinical trials and epidemiological studies
- Aspirin dose: 325 – 1000 mg per dose and max 3000 mg per day
- Literature search and text mining for identifying quantified event-specific safety information in the publications
- Analysis of adverse events/side effects presented as numbers in the publications
- Same Advisory Board used for the Lanas 2011 analysis
- Focus on endpoints presented in the Lanas 2011 analysis
  - All events from System Organ Class gastrointestinal system
  - "Minor gastrointestinal events": aggregated Preferred Terms dyspepsia, nausea/vomiting, abdominal pain
  - Preferred Terms dyspepsia, nausea/vomiting, abdominal pain individually
- Adverse events were presented descriptively
  - Incidences / odds ratios (95% CI) / risk differences (95% CI)
- Comparison to placebo and other analgesics (ibuprofen, acetaminophen)
Hangover

• “A condition consisting of a complex of symptoms involving the gastrointestinal, neurologic, and metabolic systems that follows recent acute excessive alcohol ingestion. These symptoms may include nausea, heartburn, thirst, tremor, disturbance of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability.”
CHPA Consultants

Damaris Rohsenow, Ph.D., Brown University

Jonathan Howland, Ph.D., Boston University
Analgesic/Caffeine Combination Products for Hangover

• Aspirin/caffeine (Blowfish)
• Choline salicylate/caffeine (First Aid Shot Therapy)
Clinical Investigations of Hangover Methods and Symptoms

Damaris J. Rohsenow, Ph.D.
Brown University Center for Alcohol and Addiction Studies

Jonathan Howland, Ph.D.
Boston University School of Medicine
Introduction: Hangover is well known

Well known to everyone as -
- The morning after the night before
- Pounding headache, feeling lousy

Studied with numerous surveys (most college).

About 77% of heavy drinkers or problem drinkers report getting hangover across all surveys and controlled studies (Howland et al. 2008).
Hangover: Overview of Talk

A. Definition

B. Reasons to treat

C. Methods to conduct controlled clinical investigations of hangover

D. Symptoms of hangover validated via controlled research (and mythical ones)

E. Treatment implications (briefly)
A. Definition of hangover

- **Hangover**: the unpleasant symptoms experienced after an episode of very heavy drinking that start when blood alcohol concentration (BAC) approaches zero.*
  - Not intoxication – after ETOH wears off
  - Not withdrawal – different pattern of drinking, physiology
  - Behavioral or cognitive effects we call other “residual alcohol effects”, for clarity.

- Requires peak BAC of at least .11 to .12 g%
- Requires BAC near zero when assessed: Otherwise assessing alcohol intoxication effects

*Rohsenow et al. 2012; Verster et al. 2010
Time course

- **BAC reaches near zero:** About 10 – 14 h after finishing drinking to .10-.15 g%
- **Hangover peaks** at 10-16 hours, can last 22-24 hours after drinking (10 hrs after peak), but most dissipates within 2-3 hours of peak (Ylikahri et al, 1974; Verster et al., 2010)
B. Reasons to treat hangover: Safety and economic

- **College:** can affect studying. 28% said they missed classes or work at school, 60% said often or always unable to study on hangover *
- **Workplace:** 9% of US employees have worked on hangover. Absenteeism.
- **Safety:** safety sensitive occupations might be affected by decreased accuracy when needing to act quickly.

* Verster et al., 2010
Safety implications

• About 2% slower in reaction time*. Might not matter when driving on an empty road, but in rush hour traffic? Air traffic control? Factory needing fast accurate decisions?

*Howland et al., 2010 a and b

Relief of discomfort

We treat headache and muscle ache from other causes, why not from hangover?

• “Moral” objections???
C. Controlled hangover investigation methods: How we developed these

- Started with standardly accepted alcohol administration methods used for lower doses.
- Needed to avoid confounds with alcohol intoxication, time in bed, non-specific aspects of the drinks.
- Became the standard: Our methods have been recommended by the international Alcohol Hangover Research Group (Verster et al., 2010), accepted by peer-reviewers of journals (e.g., Rohsenow et al., 2010; Howland et al., 2010), we were chosen to write a chapter on our methods for textbook *Injury Research* (Howland & Rohsenow, 2012).
Controlled hangover investigation methods: Standard accepted methods*

1. Who to enroll: heavy drinkers, past hangover
2. Facility: Beds, monitoring, nurse/EMT.
3. Dosing to target peak BAC: Aim for .11 g%, give extra alcohol if not near target.
4. Alcohol and placebo drinks given each person, order counter-balanced. Keep all methods/conditions the same except alcohol.

*Howland & Rohsenow, 2012; Rohsenow et al., 2010; Howland & Rohsenow, 2012; Verster et al., 2010.
Controlled hangover investigation methods

5. Control sleep opportunity, morning routine
   Lights out for 8 hrs.
   Do not assess hangover until BAC < .02 g%.
   Assess every hour after that.
Controlled hangover investigation methods: Potential for investigating products

- A prevention product could be given the night before, assess effects on morning symptoms.
- An alleviation product could be given as soon as arising and BAC < .02 g% - assess hangover on arising and every hour for about 6 or 8 hours.
D. Symptoms of hangover that were validated

We needed to develop a psychometrically sound measure of hangover in the moment for lab use.

Initial sources: Chapman (1970); Ylikahri et al. (1974); Seppälä et al. (1976) (controlled investigations)

- Chapman (1970) reported every symptom for every person after every peak BAC.
- Objective signs were not supported (blood pressure, heart rate; tremor, paleness, perspiration, nystagmus).
- We used symptoms reported across subjects.
We developed the “Acute Hangover Scale” *

- Unlike survey measures, asks “right now”.
- 8 most common symptoms plus a rating of “hangover” (replaces Chapman’s term “malaise” which is not in general use).
- Rated for severity: 1 (none) to 7 (incapacitating)
- Reliable: internally consistent with and without the “hangover” item. (Cronbach’s $\alpha = .84$)
- Validated each item by comparing morning after alcohol vs. placebo.

* Rohsenow et al. (2007)
# Symptoms of hangover: Validity analyses

<table>
<thead>
<tr>
<th></th>
<th>Alcohol (Mean,SD)</th>
<th>Placebo (Mean,SD)</th>
<th>Effect size $d$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hangover</strong></td>
<td>1.8 ± 1.5</td>
<td>0.0 ± 0.2</td>
<td>1.92</td>
</tr>
<tr>
<td><strong>Thirsty</strong></td>
<td>3.5 ± 1.6</td>
<td>1.9 ± 1.5</td>
<td>1.06</td>
</tr>
<tr>
<td><strong>Tired</strong></td>
<td>3.3 ± 1.5</td>
<td>2.5 ± 1.6</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>1.2 ± 1.6</td>
<td>0.2 ± 0.6</td>
<td>1.01</td>
</tr>
<tr>
<td><strong>Dizzy/faint</strong></td>
<td>0.7 ± 1.1</td>
<td>0.1 ± 0.4</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Lost appetite</strong></td>
<td>0.9 ± 1.4</td>
<td>0.3 ± 0.8</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Stomachache</strong></td>
<td>0.5 ± 1.1</td>
<td>0.1 ± 0.4</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>0.5 ± 1.3</td>
<td>0.1 ± 0.4</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Heart racing</strong></td>
<td>0.3 ± 0.8</td>
<td>0.0 ± 0.2</td>
<td>0.46</td>
</tr>
</tbody>
</table>

**Mean of items** 1.4 ± 0.9 0.6 ± 0.4 1.29

All p values < .0001. Any $d \geq .80$ is a large effect size. Items rated 0-7: 1 = mild, 4 = moderate, 7 = incapacitating (anchors)
Percent reporting each symptom: Comparing those who reported moderate hangover after drinking to BAC > .10 g% versus those who reported no hangover

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No hangover</th>
<th>Moderate Hangover</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thirsty</td>
<td>91 %</td>
<td>100 % *</td>
</tr>
<tr>
<td>Tired</td>
<td>86 %</td>
<td>100 % *</td>
</tr>
<tr>
<td>Headache</td>
<td>14 %</td>
<td>78 % **</td>
</tr>
<tr>
<td>Dizzy/faint</td>
<td>7 %</td>
<td>67 % **</td>
</tr>
<tr>
<td>Lost appetite</td>
<td>24 %</td>
<td>55 % *</td>
</tr>
<tr>
<td>Stomachache</td>
<td>7 %</td>
<td>40 % **</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 %</td>
<td>38 % **</td>
</tr>
<tr>
<td>Heart racing</td>
<td>2 %</td>
<td>27 % *</td>
</tr>
</tbody>
</table>

* p < .05; ** p < .01
Symptoms of hangover: Other validated symptoms

- Daily drinking diaries of college students for 8 weeks*, asked just 5 symptoms in a.m.: tired, headache, nauseated, very weak, difficulty concentrating on things.
- Data on 1,643 to 1,650 events.
- We compared symptoms reported the morning after drinking to $\geq 0.11$ g% vs. drinking less (estimated BAC**).
- All significantly higher after heavier drinking, p < .001.
- This adds “very weak”, “difficulty concentrating” to the list of hangover symptoms that have been validated.

*Jackson, Rohsenow, et al., 2013.
** based on #drinks, sex, weight, hours of drinking
Symptoms reported in literature that are not hangover

- **Withdrawal** symptoms: tremor, increased heart rate, increased blood pressure.
- **Intoxication** effects: e.g., trouble sleeping, memory loss/blackout (occur while high BAC).
- **Diarrhea**: never reported by any participant. Included in one early instrument*, never validated, gets repeated in the literature.
- **Emotional reactions** to having drunk excessively (e.g., guilt, suicidal, shame): thoughts about consequences of what they did, not direct effects.

*Harburg et al., 1993
Inadequate evidence for certain observable signs

Two studies did unblinded observer ratings of paleness, tremor, perspiration, nystagmus.

– Ylikahri et al. (1974) took the mean of 0-2 ratings, found it correlated with hangover (evidence for individual signs not reported).

– Seppälä et al (1976) found no effect on these same signs.

Worth additional study, currently but no evidence for any one of these signs.
Final groups of most commonly reported symptoms: all can be self-assessed

Likely different underlying processes for each:

• **Headache** (may be due to cytokines*)
• **Stomach distress** (stomach irritation?)
• **Tired, dizzy/faint, weak, trouble concentrating** (alcohol disrupts sleep in 2nd half of night**)  
• **Thirst** (diuretic effects of alcohol)

* Kim et al., 2003.  **Arnedt et al., 2011
E. Implications for Treatment

• Drinkers can identify the symptoms
• Most M.D. consensus for treating symptoms involves OTC meds, water:
  – Headache: mild anti-inflammatory pain killer
  • May be due to cytokine release
  • NEVER let heavy drinkers use acetaminophen!!!*
  – Dehydration: water (before and after sleeping)
  – Drowsiness and fatigue: caffeine, sleep
  – Stomach upset: antacids

*serious liver damage
No products for prevention can currently be recommended*

Poor or nonsignificant results for foods, vitamins
  – fructose and glucose – no effect
  – B vitamins mixed with yeast – no effect
  – Multivitamins – no effect
  – Artichoke – no effect

Many commercial products I’ve seen consist of vitamins and/or a sugar.

Weak evidence for some herbal products (KSS formula, prickly pear cactus, borage)

* That I know of
Bad basis proposed for some prevention products

E.g., SunUp: Two Yale seniors*

- Vitamins and green tea extract
- They claim it addresses the root causes of hangovers
  - Acetaldehyde – but not correlated with hangover
  - Vitamin loss – but vitamins do not affect hangover
  - Glutamine rebound – no evidence I know of
    - refer to increased blood pressure and tremors – not hangover
  - Cytokine production – good guess but premature

*New Haven Register; NBC Connecticut
F. Conclusions

- Hangovers are a definable medical condition (ICD 9 - 305; ICD 10 - F10.129)
- Hangover can be induced under controlled conditions that eliminate confounds and alternative explanations.
- Hangover symptoms can be assessed with a self-report measure.
Conclusions, cont.

• Symptoms have been identified that are greater after heavy drinking than after placebo and thus validated.
• Most common in all studies:
  1. tired (and related terms such as dizzy, faint, trouble concentrating, weak),
  2. thirsty,
  3. stomachache or nausea,
  4. headache.
Conclusions, cont.

- People may not get all of these symptoms each time they have hangover.
  - Lab: All participants who reported moderate hangover felt tired and thirsty, 78% reported headache, 67% reported feeling dizzy or faint, only 40% reported nausea/stomach ache.
  - Surveys include heavier drinking, worse hangover: Almost all reported tired/drowsy/sleepy and thirsty, 88% reported headache, 81% reported nausea*.

*Penning et al., 2010
Conclusions

• A drinker may not get all symptoms. One person might want to treat headache but not stomachache or vice versa.

• All will want to become less tired. Those with worse hangover want to treat headache and nausea as well.

• Let people identify and treat their symptoms with OTC products. They know what feels bad.

• Currently no adequate evidence for any of the marketed prevention products.
OTC Products for Hangover
Under the FDA Monograph

Joint Meeting
Nonprescription Drugs Advisory Committee
Drug Safety and Risk Management Advisory Committee
April 4, 2017
Blowfish for Hangovers

• Analgesic-stimulant combination marketed under OTC Monograph for relief of hangover symptoms
• Effervescent tablet
  – 500 mg aspirin
  – 60 mg caffeine
  – Taken with 16 oz water
• Millions of doses sold since 2011 with no SAEs

Note: Rally Labs maintains a robust pharmacovigilance program that includes an 800 number.
Consumers Seeking Hangover Relief

• 90,000 Google searches for “hangover” each month
  – More consumer interest than many common OTC indications

<table>
<thead>
<tr>
<th>Search Term</th>
<th>Monthly Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>110,000</td>
</tr>
<tr>
<td>Heartburn</td>
<td>110,000</td>
</tr>
<tr>
<td>Hangover</td>
<td>90,500</td>
</tr>
<tr>
<td>Cough</td>
<td>74,000</td>
</tr>
<tr>
<td>Congestion</td>
<td>33,100</td>
</tr>
<tr>
<td>Upset Stomach</td>
<td>27,100</td>
</tr>
</tbody>
</table>

Source: Google AdWords Keyword Planner, March 2017
Hangover Consumers

• Average age: 28\textsuperscript{(1)}
  – Relatively young, healthy population

• 80\% of target consumers aged 21 – 30 has had a hangover in the last 30 days\textsuperscript{(2)}

• Treat hangovers 2x month\textsuperscript{(2)(3)}
  – Episodic relief, not chronic use

• 82\% of hangovers are “mild to moderate”\textsuperscript{(3)}

\textsuperscript{(1)} Rally Labs customer research, 2016
\textsuperscript{(2)} Rally Labs consumer study, Jun 2016. N=500
\textsuperscript{(3)} Rally Labs website sales data, 2011-2014
Hangover Symptoms

- Expert Panel’s description of the symptom collection consistent with current consumer research and clinical studies

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>75%</td>
</tr>
<tr>
<td>Tired or sluggish</td>
<td>70%</td>
</tr>
<tr>
<td>Thirsty/feel dehydrated</td>
<td>66%</td>
</tr>
<tr>
<td>Nausea</td>
<td>52%</td>
</tr>
<tr>
<td>Upset stomach/stomach pain</td>
<td>45%</td>
</tr>
<tr>
<td>Poor or decreased sleep</td>
<td>37%</td>
</tr>
<tr>
<td>Lack of appetite</td>
<td>35%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>35%</td>
</tr>
<tr>
<td>Decreased concentration</td>
<td>34%</td>
</tr>
<tr>
<td>Sensitivity to light and sound</td>
<td>33%</td>
</tr>
</tbody>
</table>

Source: Rally Labs consumer study, Jun 2106. N=500 US Adults. Q. “Which of the following symptoms of a hangover do you usually suffer from?”
Definition Used by Expert Panel

• “noxious feelings encountered several hours after the sporadic ingestion of large amounts of alcohol”\(^{(1)}\)
  — Ethanol is no longer in the GI tract
• “...differentiated from alcoholism, an entirely different disorder encountered with chronic alcohol ingestion and the resulting pathological organ damage” \(^{(1)}\)

\(^{(1)}\) 47 FR, pg 43550
Hangover Indication in Monograph

• Bases upon which Expert Panel & FDA proposed hangover indication remain valid
  – Hangovers are a commonly recognized symptom complex
  – Long-standing history of consumers safely self-treating these symptoms with combination products
  – Clinical studies unwarranted given extensive review of individual ingredients by other panels for these precise symptoms
• Term is clear and easily understood by consumers
• Large numbers of consumers actively seeking to treat their hangover symptoms
Safety of Aspirin-Caffeine Combinations

• Extensive support for safety and efficacy of these ingredients for hangover symptoms
• Long history of use for hangovers
• No new data that affects the Panel’s recommendation
  – No SAEs, despite significant marketing history
  – No new studies that are inconsistent with the Expert Panel’s previously well-supported opinion
Clinical References

• Studies cited related to alcohol are not applicable to hangover condition
  – These studies are limited to long term, heavy alcohol abuse use or immediately after consumption¹(²)

• Studies cited related to caffeine and GI effects not applicable to monograph
  – Caffeine levels much higher than allowed dosages
  – Incorrectly conflate coffee and caffeine³(⁴)

Alternatives for Hangover Treatment

• Lack of clear hangover indication will result in more consumers using less safe alternatives:
  – Dietary supplements
    • Currently over 200 dietary supplement products listed on Amazon with illegal claims to prevent or cure hangovers
    • Most products taken before drinking
  – Self-medication
    • Pain relievers (18% use acetaminophen products)\(^{(1)}\)
    • Coffee (strong stimulator of gastric acid)

\(^{(1)}\) Rally Labs pre-market consumer research, N=305, 2006.
Aspirin-Caffeine: Safe, Rational, and Effective for Hangover Symptoms

• Widely recognized condition
• Clear consumer demand
• Aspirin and caffeine have demonstrated safety and efficacy in treating these symptoms
• No evidence to suggest these ingredients should not be used to treat hangovers
• Strongly agree with the findings of the Expert Panel that consumers should have access to this combination with a clear and specific indication for hangovers
Backup Slide
# Labeling

## Drug Facts

**Active ingredients (in each tablet)**
- Aspirin 500 mg (NSAID*)
- Caffeine 60 mg

**Purpose**
- Pain reliever
- Alertness aid
- Nonsteroidal anti-inflammatory drug

**Uses**
- 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
- Also for the temporary relief of headaches or body aches and pains alone

**Warnings**
- Reye’s syndrome: Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye’s syndrome, a rare but serious illness.
- Allergy alert: Aspirin may cause a severe allergic reaction which may include: hives, facial swelling, asthma (wheezing), shock.
- Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause severe stomach 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, or take other drugs containing

## Drug Facts (continued)

- Prescription or non-prescription 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

**Do not use**
- If you have ever had an allergic reaction to aspirin or any other pain reliever/fever reducer

**Ask a doctor before use if**
- Stomach bleeding warning applies to you
- You have a history of stomach problems, such as heartburn
- You have high blood pressure, heart disease, liver disease, liver cirrhosis, or kidney disease
- You are taking a diuretic
- You have asthma
- You have a sodium-restricted diet

**Ask a doctor or pharmacist before use if you are**
- Taking a prescription drug for diabetes, gout, arthritis

**Caffeine warning**
- The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages because too much caffeine may cause nervousness, irritability, sleeplessness, and occasionally rapid heart beat. For occasional use only.

**Stop use and ask a doctor if**
- An allergic reaction occurs. Seek medical help right away
- You experience any of the following signs of stomach bleeding: feel faint, vomit blood, have bloody or black stools, have stomach pain that does not get better, pain lasts for more than 10 days or gets worse
- New symptoms occur: redness or swelling is present, ringing in the ears, or a loss of hearing occurs

**If pregnant or breastfeeding**
- Ask a health professional before use. It is especially important not to use aspirin during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

## Other Information
- Each tablet contains: sodium 406 mg
- Phenylketonurics: contains phenylalanine 12.6 mg per tablet
- Store at room temperature (59-86°F)
- Protect from excessive heat

## Inactive ingredients
- Acesulfame potassium, anhydrous citric acid, aspartame, docusate sodium, flavors, mannitol, povidone, sodium benzoate, sodium bicarbonate

**Questions or Comments?**
1-800-970-1793 (weekdays)

forhangovers.com

**DO NOT USE IF PRINTED PACKETS ARE TORN OR PUNCTURED**
Summary

• Aspirin/antacid combinations for treatment of pain with upset stomach have a favorable safety profile.
• Hangover is an appropriate indication under the OTC monograph and should remain.