Acetaminophen: Background and Overview

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Acetaminophen

- One of the most widely used medicines in the US
  - Treatment of pain and fever
  - Found in many prescription and over-the-counter preparations
  - 24.6 billion doses*,[1] sold in 2008
- Safe and effective when used according to directions on OTC and Rx labeling
- Also known as “APAP” and “paracetamol”

*1 dose = 1 tablet = 5 mL liquid = 1 mL conc. drop

[1] IMS Health, IMS National Sales Perspectives, Year 2004 – 2008, Extracted 4/09

Acetaminophen-induced Hepatotoxicity

- A persistent important public health problem
- Usually related to exceeding the maximum daily dose (4 gm/day)
  - Both unintentional and intentional
  - Both prescription and OTC preparations
- A leading cause of drug-induced liver injury
  - 51% of acute liver failure cases in 1998-2003 from a multicenter study (Larson et al. Hepatology 2005; 42:1364-1372)
  - CDC estimate from 2007: 1600 cases of ALF in US (all causes). Acetaminophen was the most common etiology.

FDA's Attempts to Mitigate Hepatotoxicity Risk

- 1998 – Final rule on adding alcohol warning to OTC labeling
- 2002 – Advisory Committee meeting
  - Focus = unintentional overdose
  - Recommendations:
    - Specific liver toxicity warning
    - Distinctive OTC labeling to more readily identify acetaminophen as an ingredient
    - Educate consumers and healthcare professionals about potential for liver injury

FDA's Outreach Efforts

- 2004 Educational Campaign
  - Goal: safe use of NSAIDs and acetaminophen
  - Ongoing effort
- 2004 – Contact state boards of pharmacy
  - Asked that prescriptions use the term "acetaminophen", not "APAP"
  - Instruct patients
    - not to use other acetaminophen-containing products
    - Instruct patients not to exceed the maximum recommended daily dose
    - To avoid drinking alcohol during prescription acetaminophen use
  - As of February 2008, suggestions not implemented

Recent FDA Efforts

- 2007 CDER-wide Working Group
  - To review safety issues related to acetaminophen
  - Consider additional steps to reduce acetaminophen-related liver injury
  - Need for public discussion recognized
- 2009 – Final rule for OTC acetaminophen labeling
  - Strengthened liver-related warnings
  - Ingredient name (ie, acetaminophen) is more prominent
  - Warning to avoid other acetaminophen-containing products

The Main Issue

- What specific steps can be taken to reduce acetaminophen-related liver injury?
- FDA will present a series of options for discussion today and tomorrow
- FDA is considering options, but has not yet decided on any
- FDA is open to hearing other options

Approach to the Options

- Potential to decrease incidence of liver injury?
- Effect on patients?
- Effect on healthcare practitioners?
- Resources necessary to implement it?
- Steps that manufacturers need to take?
- Other potential consequences?
- Prioritization of the options

Putting the Options into Context

- Safe use of acetaminophen requires engagement of all involved parties
  - Patients
  - Prescribers
  - Pharmacists
  - Regulators
  - Industry
- Regulatory action may be needed, but it will not be sufficient

Overview of the Options

- Option 1
  - Reduce current doses (eg, current maximum adult daily dose, single adult dose, and tablet strength), or restrict current maximum adult daily dose, single adult dose, and tablet strength to prescription only
- Option 2
  - Establish package size limits for OTC acetaminophen products
- Option 3
  - Require unit-of-use packaging for prescription products

Overview of the Options (cont.)

- Option 4
  - Expand product warning information on prescription products
- Option 5
  - Eliminate combination OTC or prescription products that contain acetaminophen
- Option 6
  - Limit dosing formulations for OTC liquid products; require dosing device

Overview the Meeting

- Presentations
  - FDA and FDA's invited speakers
    - Regulatory
    - Marketing and Usage
    - Metabolic/toxicology
    - Safety
    - Efficacy
    - OTC Usage
    - Educational efforts
    - United Kingdom Experience
  - Industry
- Open Public Hearing
- Discussion
- Voting

Thank You

Regulation of Acetaminophen Drug Products

Joint Meeting of the Drug Safety and Risk Management, Nonprescription Drugs, and the Anesthetic and Life Support Drugs Advisory Committees

College Park, Maryland

June 29 & 30, 2009

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Outline

- Regulatory Mechanisms
  - R_x: NDA / ANDA
  - OTC: NDA / ANDA & Monograph
- OTC Regulatory History
  - Dosage
  - Combinations
  - Labeling related to liver injury

Regulatory Mechanisms

NDA / ANDA

- Regulatory process for
  - All R_x drugs, some OTC drugs
    - Drug product specific
    - Requires pre-approval
    - Mandated timelines

R_x Combination Products

Ingredient(s)	Uses
•Codeine •Dihydrocodeine •Hydrocodone •Oxycodone •Propoxyphene •Pentazocine •Tramadol	•Moderate to severe pain
•Butalbital	•Tension headache

Doses: 325-750 mg acetaminophen per tablet for single doses of 325 – 1000 mg

OTC Monograph

- OTC drugs under the OTC Drug Review
  - Multistep rulemaking process (requires public notice and comment)
  - Category specific (e.g., antacid, decongestant, etc.)
  - Establishes conditions for use for ingredients determined to be Generally Recognized As Safe and Effective (e.g., dose, labeling, testing)
  - Manufacturers follow the conditions of use provided for in the monograph for marketing
  - No pre-approval required

Multi-Step Rulemaking Process

Comments

Data

Comments

Data

Panel's Report ***Proposed Rule*** ***Final Rule***

Regulatory Events

Early Regulatory History

1977	Advance Notice of Proposed Rulemaking
1988	Proposed Rule

Established initial conditions:

- Safe and effective dosage
- Indications for use
- Combination products

OTC Adult Dosing Schedule

Regulation	Dosage Unit	Frequency	24 Hour Maximum Dosage
Monograph	325 mg	1-2 tablets every 4 hours	3,900 mg
Monograph	500 mg	1-2 tablets followed by 500 mg every 3 hours or 1000 mg every 6 hours	4,000 mg
NDA	650 mg*	2 tablets every 8 hours	3,900 mg

*Approved in 1994

OTC Combination Products

Type	Ingredient(s)	Use
Analgesic/ Antipyretic	•Aspirin	Pain reliever/ fever reducer
Cough/ Cold	•Antitussive •Antihistamine •Nasal Decongestant •Expectorant	Sore throat Sinus congestion Sneezing Allergy Runny nose Flu symptoms
Stimulant	•Caffeine	Migraine Headache
Antacid	•Citric Acid	Overindulgence
Diuretic	•Parabrom	Menstrual symptoms

Regulatory History Related to Liver Injury

1993	Advisory Committee Meeting (Alcohol Use/Abuse)
1997	Proposed Rule (Alcohol Warning)
1998	Final Rule (Alcohol Warning)
2002	Advisory Committee Meeting (Liver Injury)
2004	Public Information Campaign (FDA & Partners)
2006	Proposed Rule (Liver Warning)
2009	Final Rule (Liver Warning)

Citizen Petition

- PPSI, November 2006
  - Mandate that OTC acetaminophen products clearly state:
    - "contains acetaminophen – do not take with any other acetaminophen/APAP product"
  - Use blister packaging
  - Restrict pack size limit
    - 8 or 16 gm total content
  - Behind-the-counter status
  - MedGuide/Black box warning detailing recommended dosages and risks

PDP for Single Ingredient Products

Required Labeling
Principal Display Panel (PDP)

- Single Ingredient Products
  - Ingredient name (i.e. acetaminophen) highlighted or in bold type
  - “Acetaminophen” prominently displayed (at least ¼ as large as the most prominent printed matter)
  - Statement "see new warnings information" is required on the front of the carton for one year from the date the final rule was published

Combination Product Required PDP Labeling

Required Labeling
Principal Display Panel (PDP)

- Combination Ingredient Products
  - Other types of combination products are not required to list the ingredients in the formulation
  - For acetaminophen combination products, the names of all the active ingredients must appear
    - "Acetaminophen" must be highlighted or bolded and in a prominent size
    - "See new warnings information" statement required

Drug Facts

Active ingredient (in each tablet) — **Purpose**

Acetaminophen 325 mg ..... Pain reliever/fever reducer

- temporarily relieves minor aches and pains due to:
  - headache
  - backache
  - muscular aches
  - toothache
  - the common cold
  - minor pain of arthritis

Warnings

Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take

- more than [*insert the maximum number of daily dosage units*] in 24 hours, which is the maximum daily amount
- with other drugs containing acetaminophen
- 3 or more alcoholic drinks every day while using this product

Do not use with any other product containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a

Ask a doctor before use if you have liver disease

Ask a doctor or pharmacist before use if you are taking the blood thinning drug warfarin

[*insert other required warnings*]

Directions

[*insert product-specific dosing*]

Other information

[*insert product-specific information such as storage conditions*]

Inactive ingredients

[*insert ingredients in alphabetical order*]

Questions or comments?

[*insert toll-free phone number and/or website*]

Summary

- Prescription acetaminophen products are regulated under NDAs/ANDAs. All prescription acetaminophen products are combination products.
- Most acetaminophen OTC products are regulated under the OTC monograph.
- The 1988 Proposed Rule (not final) establishes
  - Maximum daily dose for adults as 4,000 mg
  - Various combinations of OTC ingredients
- The 2009 liver warning final rule addresses important safety issues for the safe use of acetaminophen
  - Easier recognition of acetaminophen as an ingredient in products
  - Provides awareness of liver injury risk to consumers
- Changes to the current (1988) acetaminophen proposed rule require a proposed rule followed by a final rule.

OTC and Rx Acetaminophen Market Overview Years 2004 - 2008

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June 29, 2009

Outline

- Overall acetaminophen products sales trend
- OTC acetaminophen product sales
- Rx acetaminophen combination dispensed prescriptions
- Summary

National OTC sales data
IMS Health, IMS National Sales Perspectives™

- Measures the volume of prescription (Rx) and over-the-counter (OTC) products sold from manufacturers to retail and non-retail channels of distribution
  - **Eaches (EA)** are the number of packets, bottles, and vials of a product shipped in a unit
  - **Doses** were calculated from Extended Units as 1 tablet = 1 dose; 5 mL liquid = 1 dose; 1 mL conc. drop = 1 dose
  - **Total Dollars** measures the amount of money pharmacies, non-federal hospitals, federal facilities, long-term care facilities, clinics, and HMOs spent on a product acquired from manufacturers and drug wholesalers.

Overall acetaminophen market: OTC and Rx sales, Y2004 - Y2008

- 28% growth in overall acetaminophen market between Y2004 and Y2008
- Over 370 million bottles and packets, or 24.6 billion doses* sold in Y2008 (~$2.6 billion in sales)
- Nearly 80% of entire market is OTC products (~$1.15 billion in sales)
  - OTC combination ~50%
  - OTC single-ingredient ~30%
- Proportion of Rx acetaminophen market steady at ~20% of overall acetaminophen market (~$1.4 billion in sales)

*Doses: 1 tablet = 1 dose; 5 mL liquid = 1 dose; 1 mL conc. drop = 1 dose

Sale of OTC and Rx acetaminophen containing drug products, in Eaches, from manufacturers to retail and non-retail pharmacies, Y2004 – 2008

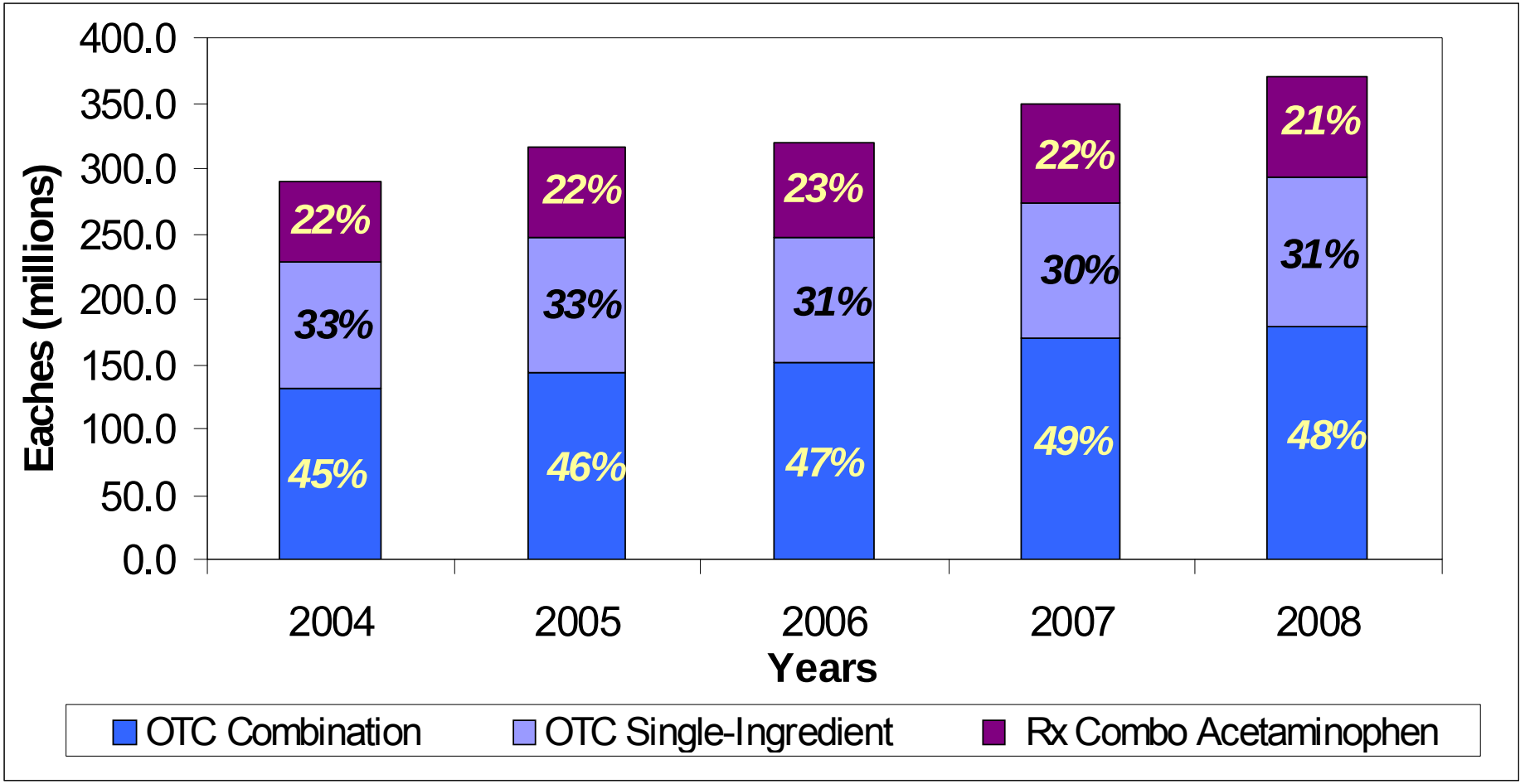
IMS Health, IMS National Sales Perspectives, Extracted 4/09

	Eaches (in millions)					*% Change from 2004 to 2008*
	2004	**2005**	**2006**	**2007**	**2008**	
Rx and OTC acetaminophen products	290.2	316.4	319.7	349.1	370.2	*28%*
OTC acetaminophen	227.9	247.8	247.9	274.0	292.3	*28%*
OTC Combination	131.3	144.0	150.5	169.9	178.2	*36%*
OTC Single-Ingredient	96.6	103.8	97.5	104.1	114.1	*18%*
Rx Combo acetaminophen	62.3	68.6	71.8	75.1	77.9	*25%*

IMS Health, IMS National Sales Perspectives™, Years 2004 – 2008

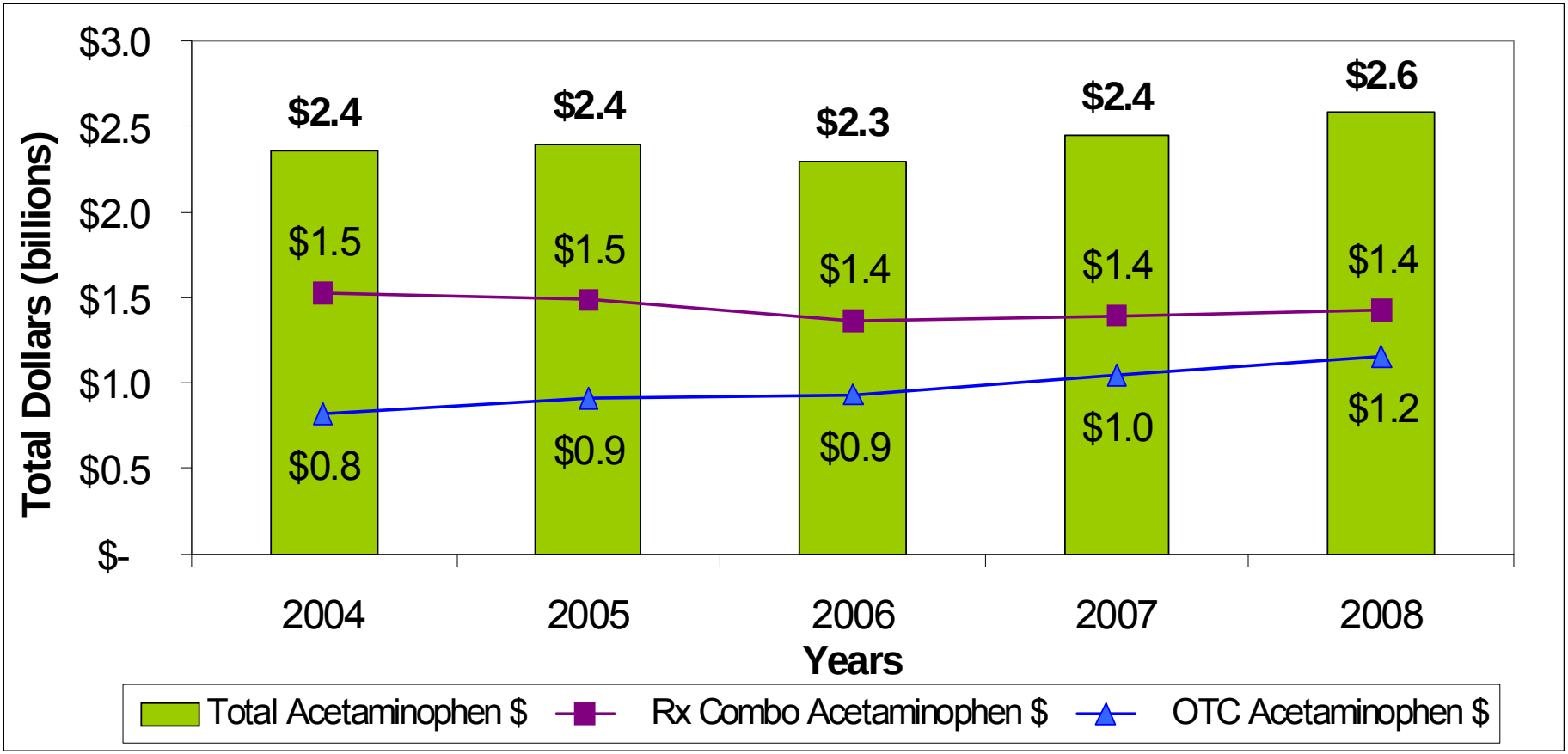
Total number of bottles or packets (Eaches) sold for acetaminophen containing products in the U.S., Years 2004 – 2008

IMS Health, IMS National Sales Perspectives, Extracted 4/09



Total sales dollars for acetaminophen containing products in the U.S., Y2004- 2008

IMS Health, IMS National Sales Perspectives, Extracted 6/09



Over-The-Counter (OTC) Acetaminophen Products

Combination and Single-Ingredient

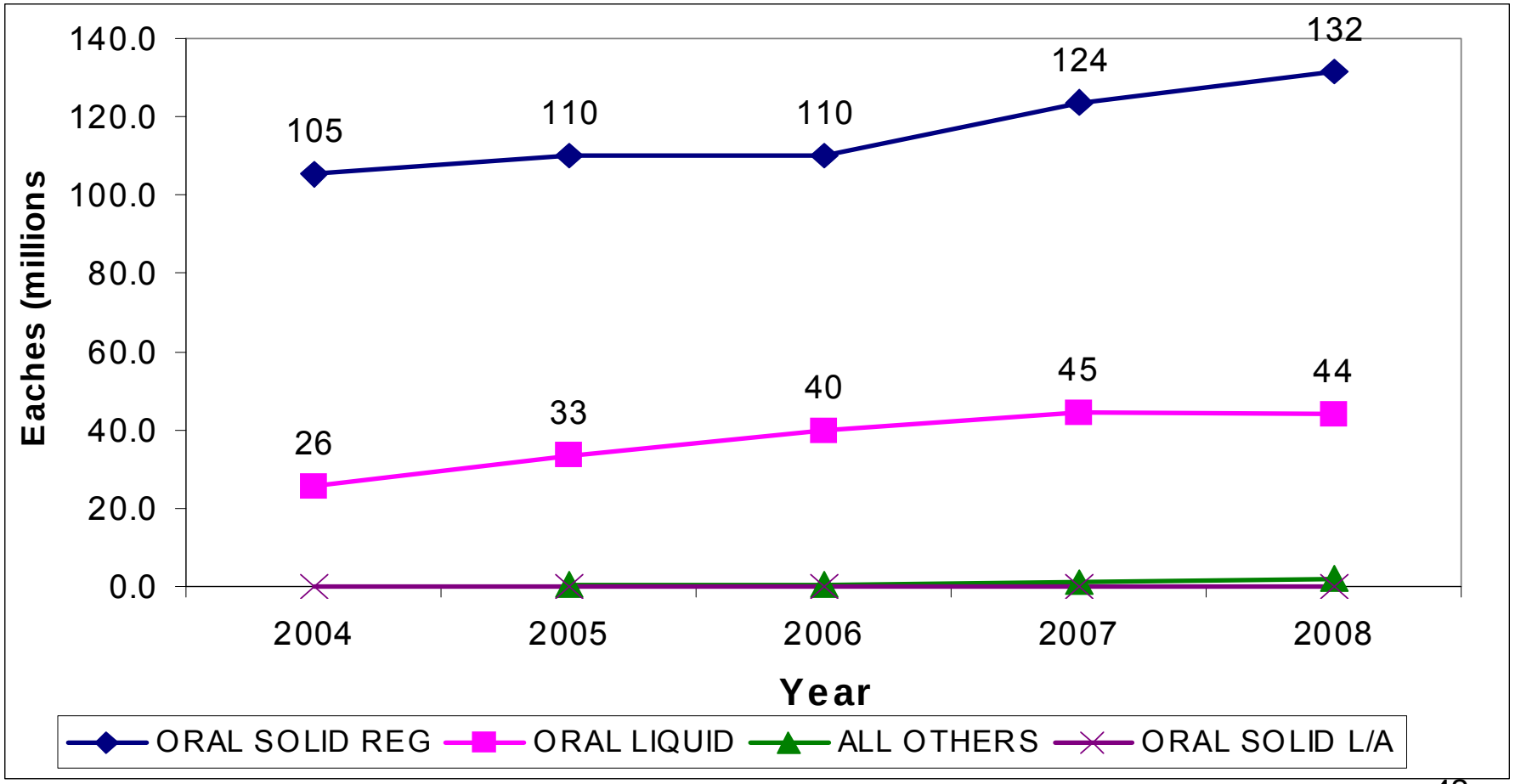
OTC combination acetaminophen product sales

IMS Health, IMS National Sales Perspectives, Extracted 4/09

- Nearly 60% of all OTC products are combination products
  - 36% increase in sales between Y2004 & Y2008
  - Oral solid formulations account for ~75% of product sales for Y2008
  - Liquid formulations account for ~25% of product sales for Y2008
    - Combination oral concentrated drops declined from 12% of liquid formulation sales in Y2004 to 0% in Y2008 due to voluntary withdrawal by manufacturers

Sale of OTC combination acetaminophen products by dosage form, Y2004 – 2008

IMS Health, IMS National Sales Perspectives, Extracted 4/09



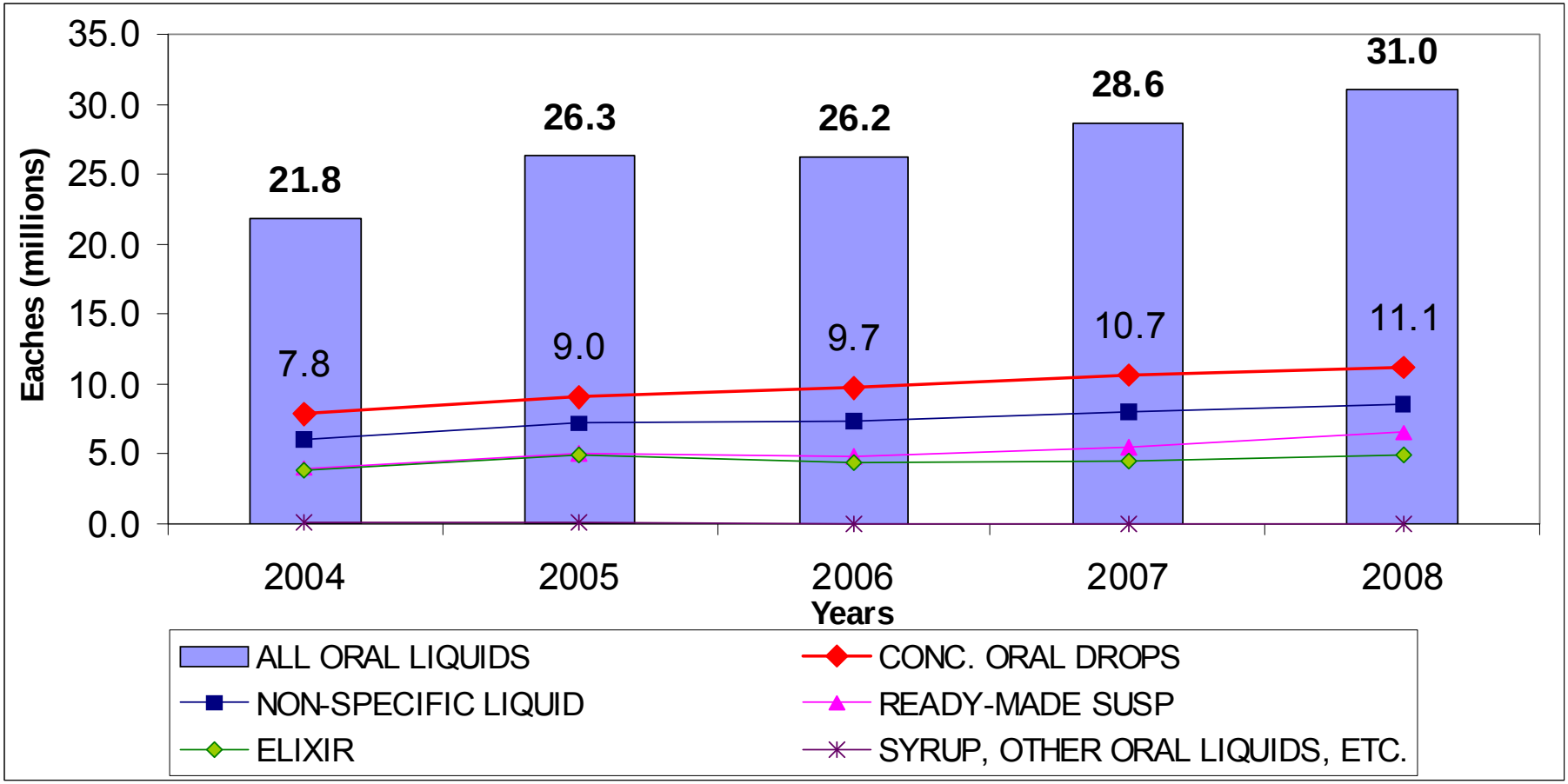
OTC single-ingredient acetaminophen product sales

IMS Health, IMS National Sales Perspectives, Extracted 4/09

- Single-ingredient OTC products make up ~40% sales volume
  - 18% increase in sales between Y2004 & Y2008
  - Oral solid formulations account for ~63% of product sales for Y2008
  - Oral liquids formulations account for ~27% of product sales for Y2008
    - Proportion of concentrated oral drops steady at ~36% of all oral liquid sales
  - Oral solid long-acting formulations account for ~9% of product sales for Y2008

Sale of single-ingredient oral liquid formulations, Y2004 – 2008

IMS Health, IMS National Sales Perspectives, Extracted 4/09



Most commonly sold strength of OTC acetaminophen products from manufacturers, Y2008

IMS Health, IMS National Sales Perspectives, Extracted 6/09

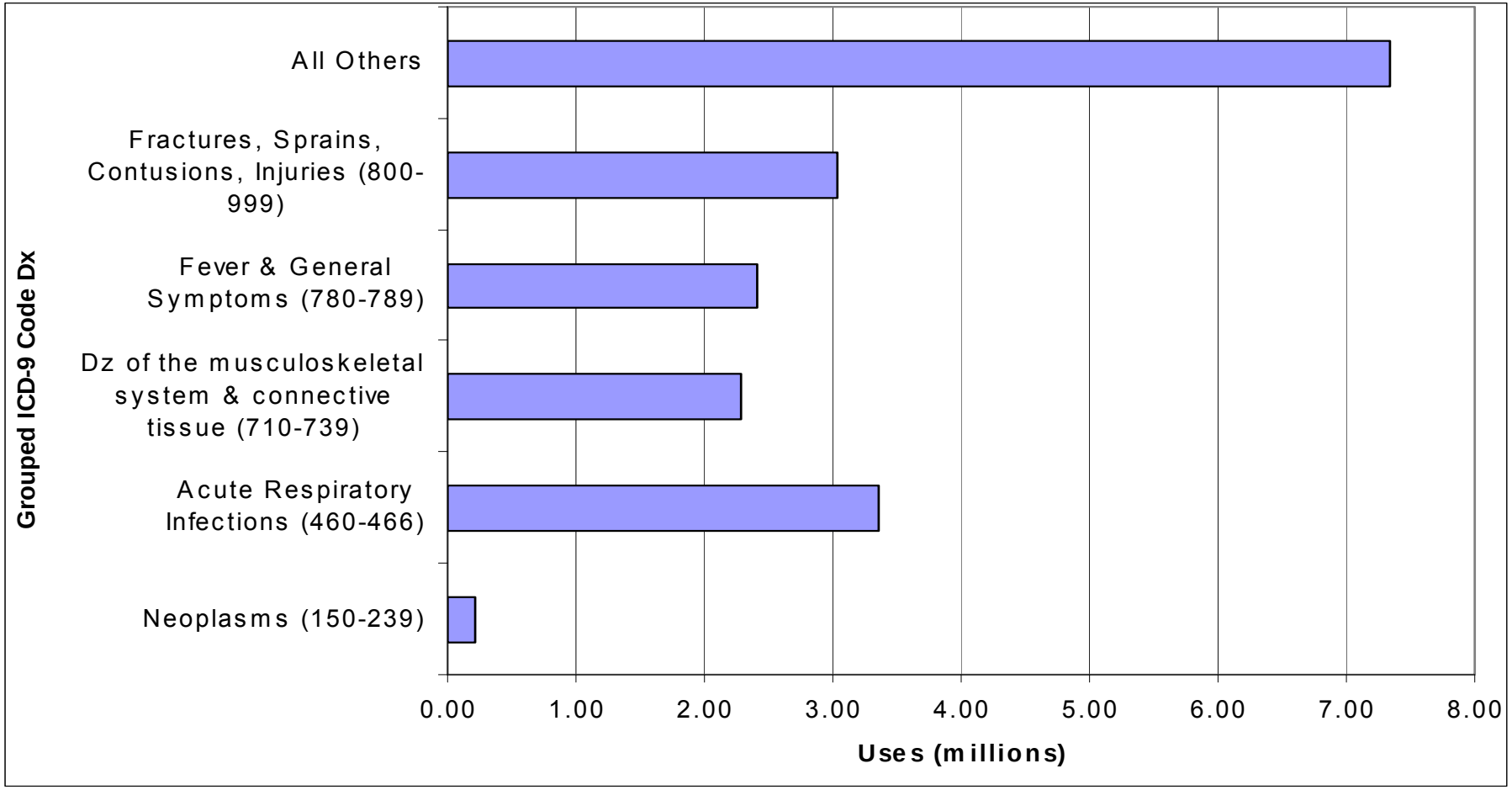
OTC Combination	%	OTC Single-Ingredient	%
325 mg	30	500 mg	47
500 mg	20	160 mg	15
250 mg	13	650 mg	10
160 mg	6	100 mg	10
650 mg	3	325 mg	9
Unknown/Indeterminate	28	All Others	10

Diagnoses associated with use SDI, Physician Drug and Diagnosis Audit™

- Office-based physician survey data
  - monthly survey composed of approximately 3,100 office-based physicians that monitors disease states and the physician intended prescribing habits on a national-level
  - designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S.
  - represents 29 specialties across the United States

Diagnoses associated with the use of single-ingredient acetaminophen products by grouped ICD-9 codes, Year 2008

SDI, Physician Drug and Diagnosis Audit™, Extracted 6/09



Rx acetaminophen (combination) products

National dispensed prescription data SDI, Vector One®: National (VONA)

- SDI's Vector One®: National (VONA) is a national-level projected prescription and patient-centric tracking service.
  - Receives over 2.0 billion prescription claims per year, representing over 160 million unique patients
- The number of dispensed prescriptions is obtained from a sample of approximately 59,000 pharmacies throughout the U.S., accounting for nearly all retail pharmacies and representing nearly half of retail prescriptions dispensed nationwide
- Retail pharmacies include: national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups

Rx acetaminophen market, Year 2008

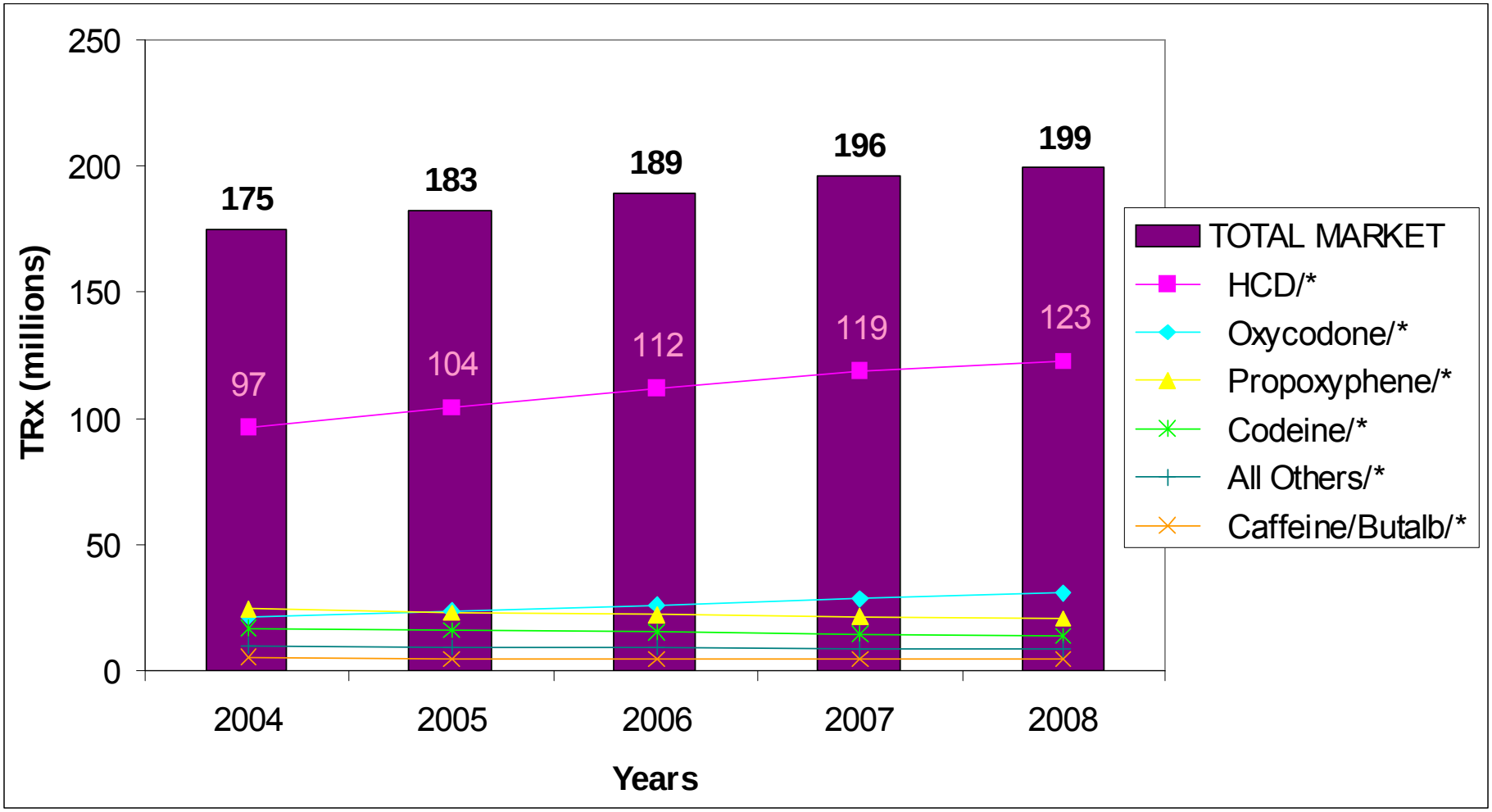
SDI, Vector One®: National. Extracted 6/09

- Nearly 200 million dispensed prescriptions for Rx acetaminophen containing products in Y2008
  - Hydrocodone/acetaminophen products ~123 million Rx (62%)
  - Oxycodone/acetaminophen products ~31 million Rx (15%)
  - Propoxyphene/acetaminophen ~21 million Rx (10%)
  - Codeine/acetaminophen ~13.5 million Rx (7%)

- Non-narcotic Rx acetaminophen combination products account for ~5% of market
  - Acetaminophen/Caffeine/Butalbital ~4.5 million Rx (2%)
  - Tramadol/acetaminophen ~3.2 million Rx (2%)

Total number of prescriptions dispensed for the top five Rx acetaminophen* containing products, Y2004 – 2008

SDI, Vector One®: National. Extracted 6/09



Most commonly dispensed strength of acetaminophen in prescription combination acetaminophen products, Y2008

	%
TOTAL	***100.0%***
750 mg	*7%*
660 mg	*<1%*
650 mg	*9%*
600 mg	*0.0%*
500 mg	***40%***
400 mg	*0.0%*
325 mg	*13%*
300 mg	*6%*
<250 mg	*9%*
unknown	*15%*

- **~16%** of dispensed prescriptions for combination-acetaminophen products were for strengths **greater than 500 mg** of acetaminophen
- **~40%** were for **500 mg** strengths of acetaminophen
- **~29%** were for strengths **less than or equal to 325 mg** of acetaminophen

Limitations

- Approximately 50% of all OTC sales captured by IMS, National Sales Perspectives™
- Using sales volume as surrogate for use
  - Unable to determine user demographics
  - Unable to determine frequency or amount of OTC products used at the consumer level
  - Unable to determine concurrent product use
- “Drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned.

Summary…

- Sale of Rx combination and OTC acetaminophen products growing in terms of units sold and dollars
- Most commonly sold OTC acetaminophen strength
  - Combination OTC is 325 mg
  - Single-Ingredient OTC is 500 mg
- Majority of dispensed Rx combination acetaminophen products are 500 mg or greater of acetaminophen

Characterization of Acetaminophen Overdose and Related Hepatotoxic Events

Joint Meeting of the Drug Safety and Risk Management, Nonprescription, and Anesthetic and Life Support Drugs Advisory Committees

Office of Surveillance & Epidemiology

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Objectives

Objective 1. To characterize the intentionality of acetaminophen overdoses, and to provide national estimates of emergency department visits and hospitalizations that are overdose-related.

Objective 2. To describe the burden of acetaminophen-associated calls to the National Poison Data System.

Objective 3. To provide a perspective on the magnitude of liver toxicity associated with acetaminophen in the US and to characterize unintentional overdoses.

Methods

Objective 1. To characterize the intentionality of acetaminophen overdoses, and to provide national estimates of emergency department visits and hospitalizations that are overdose-related.

***Methods*.** Utilized two publicly available data sources:

- National Hospital Ambulatory Care Survey - Emergency Department (NHAMCS-ED)
  - Descriptive analyses calculating weighted frequencies of ED visits
- National Hospital Discharge Survey (NHDS)
  - Calculated age adjusted hospitalization rates (≥10 years of age) standardized to US population in 2000
  - Calculated crude hospitalization rates by intentionality using US population as denominator

Definitions

Acetaminophen overdose-related ED visits & hospitalizations

•Includes *all* ED visits or hospitalizations ICD-9 coded for acetaminophen-poisoning

Intentionality

• NHAMCS (Emergency Department)

-- Intentionality determined using survey question

• NHDS (Hospitalizations)

-- Intentionality determined using ICD-9 codes

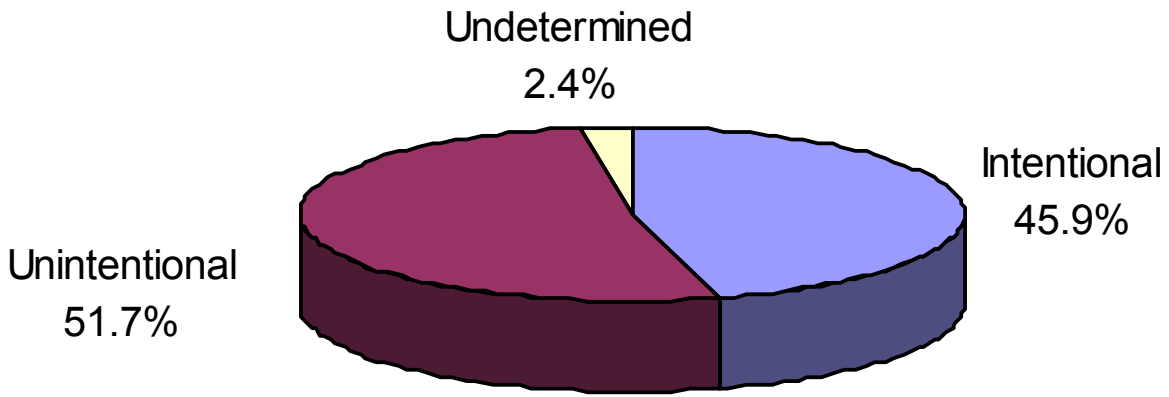
Intentional: hospitalization coded for acetaminophen-poisoning and coded for suicide or overdose due to other substances

Unintentional: hospitalization coded for accidental acetaminophen-poisoning with no coding for suicide, overdose due to other substances, or depressive disorder

Undetermined: all remaining hospitalizations coded for acetaminophen-poisoning

Acetaminophen overdose-related Emergency Department Visits

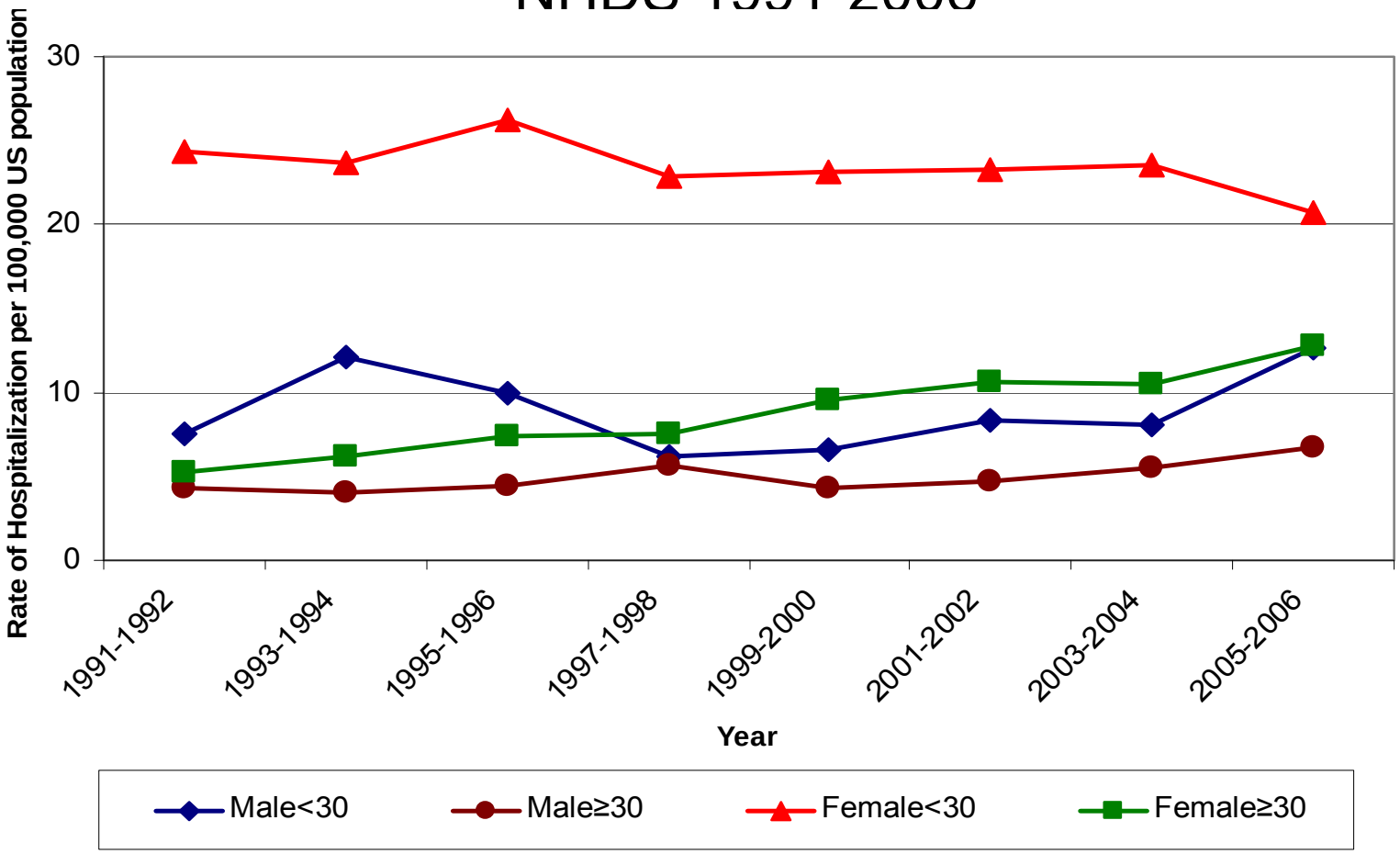
- Average No. of Visits per year for 2000-2006* = 42,329



Intentionality defined using survey question “Is this injury/poisoning intentional?”

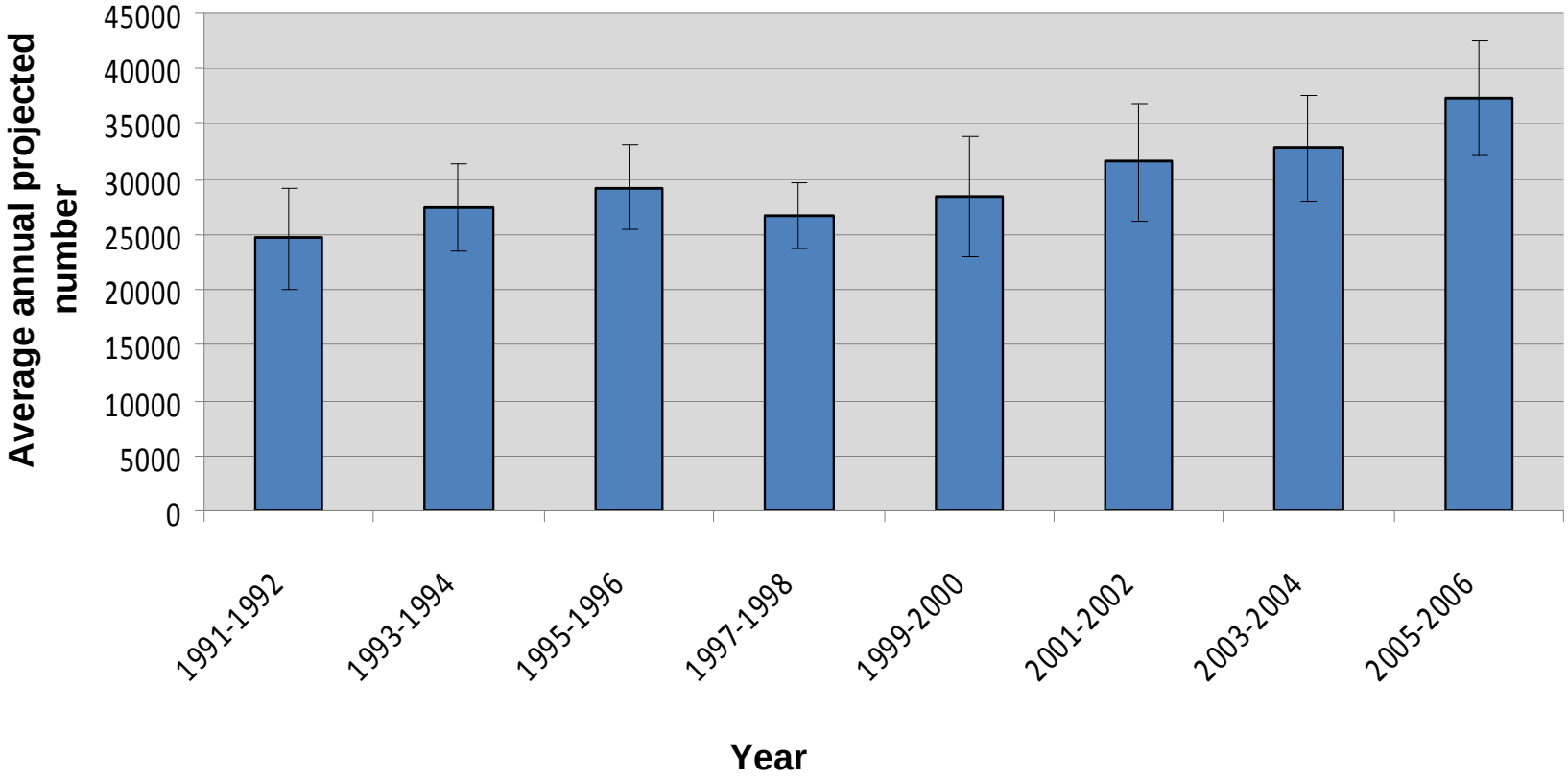
* NHAMCS data

Crude rate of acetaminophen overdose-related hospitalizations* in the United States by age and sex: NHDS 1991-2006



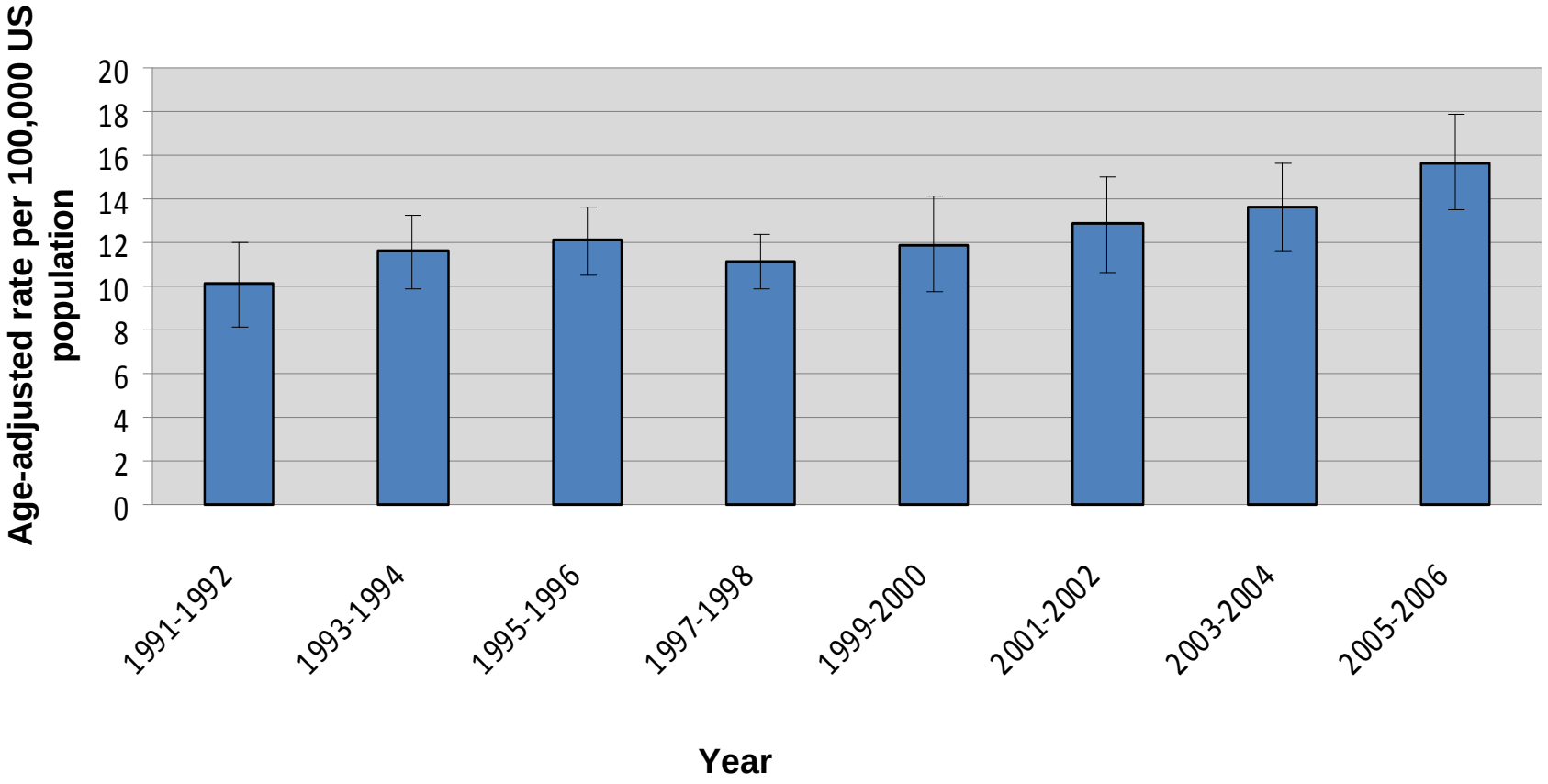
*Each estimate represents the average number of hospitalizations over a two-year period.

Nationally projected number of acetaminophen overdose-related hospitalizations* in the United States: NHDS 1991-2006



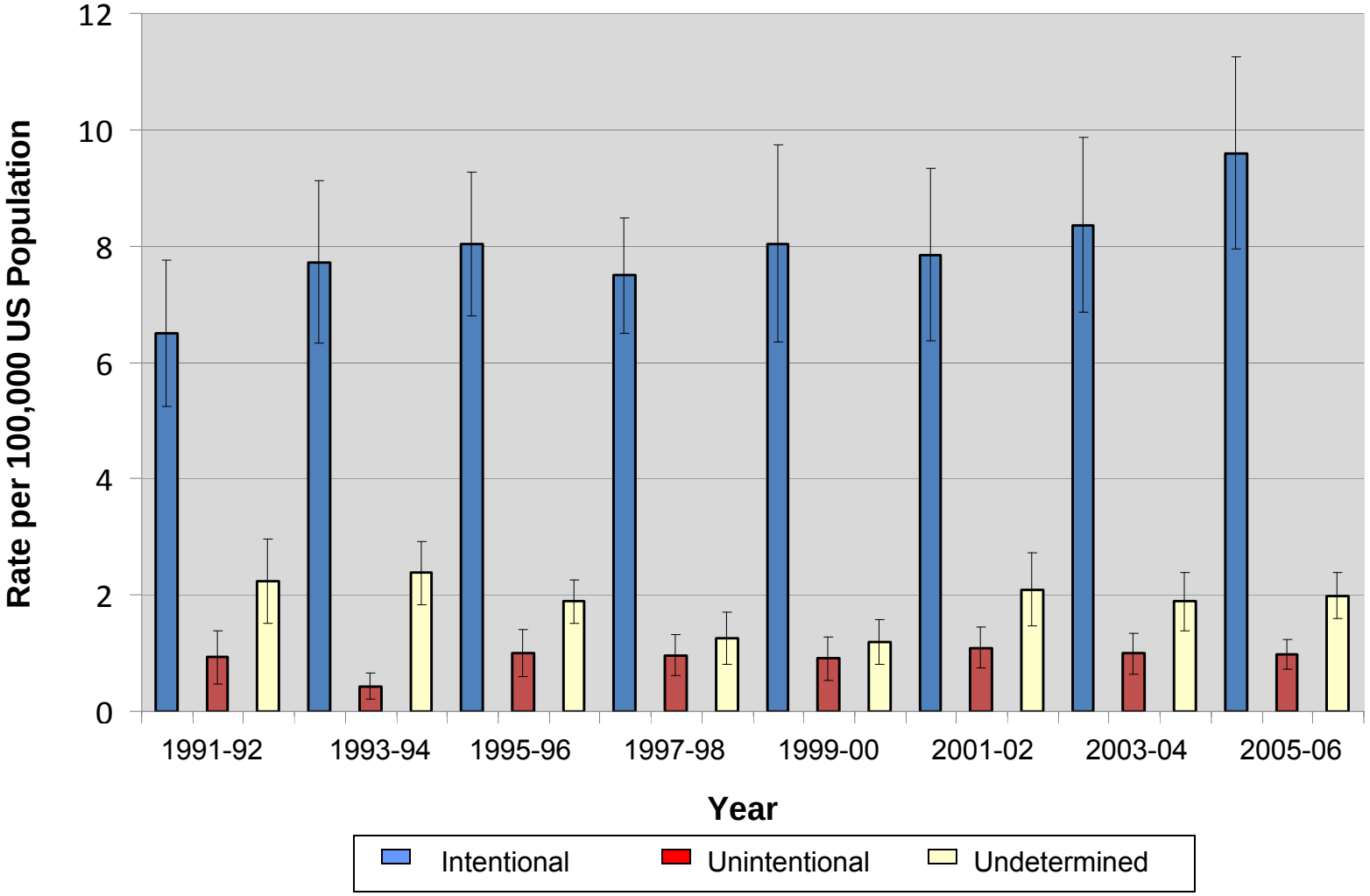
*Each estimate represents the average number of hospitalizations over a two-year period.

Age-adjusted rate of acetaminophen overdose-related hospitalizations* in the United States population aged 10 years and older: NHDS 1991-2006



*Each estimate represents the average number of hospitalizations over a two-year period standardized to the US population in 2000.

Crude rate of acetaminophen overdose-related hospitalizations* in the United States by intentionality: NHDS 1991-2006



*Each estimate represents the average number of hospitalizations over a two-year period.

Limitations

- National Center for Health Statistics states crude counts <30 should not be reported because the estimate is considered unreliable
- Limited data on liver toxicity
- No information on type of product (single-ingredient vs. combination; OTC vs. Rx)
- Intentionality difficult to ascertain
  - Social stigma associated with suicide may result in intentional cases being misclassified as unintentional.
  - Accidental poisonings (E-code) incompletely reported in NHDS due to differential reporting requirements by states

Methods

Objective 2. To describe the public health burden of Acetaminophen-associated calls to the National Poison Data System (NPDS).

Methods. Utilized publicly available published annual reports:

- NPDS, the poisoning database of the American Association of Poison Control Centers
  - Reviewed annual reports from 2003-2007
  - Reported number of calls, and number of calls resulting in fatalities
  - For fatality reports, included only cases listing acetaminophen as the primary (first) agent.

Definitions

Acetaminophen-related fatalities

- Death that was judged by the Poison Control Fatality Review Team to be related to acetaminophen

Intentionality

- Intentional
  - suspected suicide
  - intentional abuse, and
  - intentional unknown
- Unintentional
  - unintentional general
  - intentional misuse
  - unintentional misuse
  - therapeutic error, and
  - adverse drug reaction

Summary of Calls

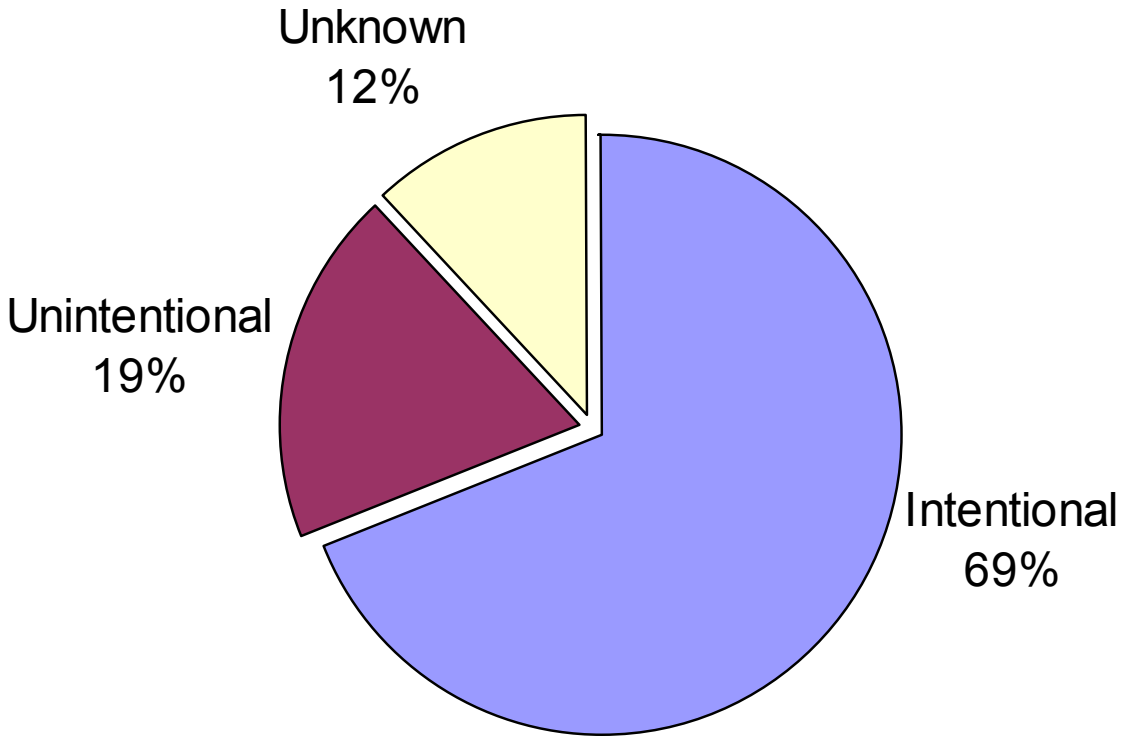
- In 2005, acetaminophen poisoning-associated calls represented 5% of all calls to Poison Control Centers.
- Total number of calls increased slightly from 105,480 in 2003 to 116,613 in 2005.
- Of 116,613 total calls in 2005:
  - 61,249 (52%) required treatment in health care facilities
  - 2,698 (2%) related to signs and symptoms that were life threatening or resulted in significant disability
  - 43,122 (37%) involved children (< 6 years)
  - 69,786 (60%) involved unintentional exposures

Fatalities

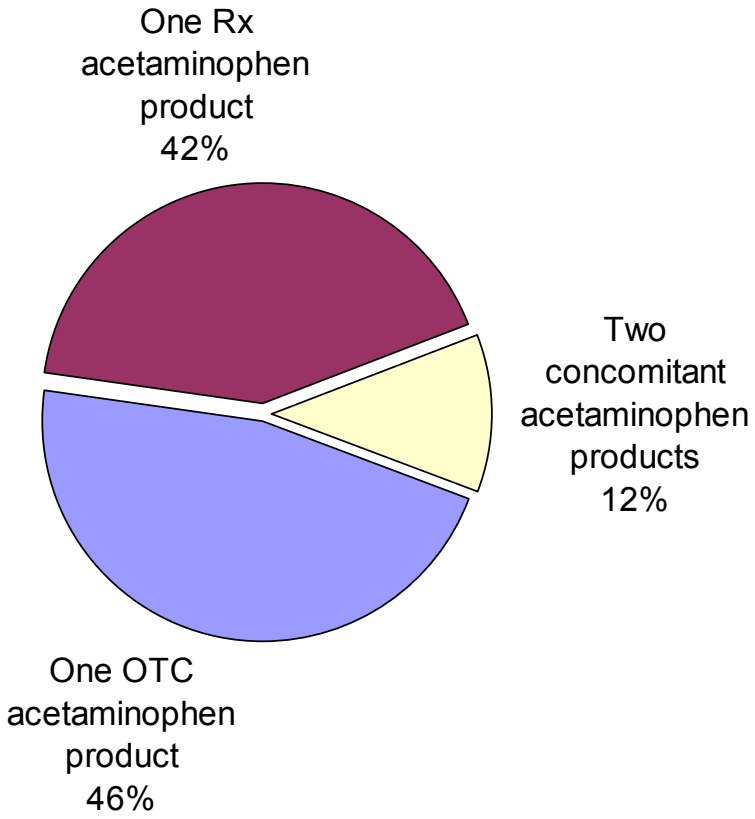
- Total number of acetaminophen-associated calls involving a fatality reported to NPDS in 2003 was 214; increased to 224 in 2007.*
- Acetaminophen-associated fatalities represented 18% of the 1,239 total calls involving fatalities reported to NPDS in 2007.
- Of the 224 fatalities in 2007, acetaminophen was
  - "undoubtedly responsible" in 124 (55%) of cases
  - "probably responsible" in 83 (37%) of cases
  - "contributory" in 17 (8%) of cases

* The definition of fatality (attribution of a death to the exposure) changed in 2006

Intentionality Among Acetaminophen-related Fatalities Reported to the National Poison Data System in 2007 (n=224)



Root Cause Of Unintentional Acetaminophen-related Fatalities Reported to National Poison Data System in 2007 (n=43)



Limitations

- Underreporting may be extensive
  - Serious cases may go directly to EDs and may not be captured by poison control centers (PCCs)

- Chronic users may be less likely to call the PCC and thus not be captured

Methods

Objective 3. To provide a perspective on the magnitude of liver toxicity associated with acetaminophen in the US and to characterize unintentional overdoses using representative cases.

Methods. Utilized the following data source:

- Adverse Event Reporting System (AERS)
  - Analysis of the most common drug associated with liver failure from 2004 – 2008
  - Key findings from a review of acetaminophen and hepatotoxicity, 2002
  - Characterize unintentional overdoses using representative cases

AERS Reports Associated with Liver Toxicity*

- Analysis of drugs associated with the highest number of reports of liver failure for the years 2004 to 2008**
  - Acetaminophen continues to be the number one drug with reports of liver failure in AERS.
- AERS continues to receive reports of liver toxicity and death associated with acetaminophen***

*The analysis was based on crude counts - no individual review was performed. Crude counts may contain duplicate reports and there is no certainty that the suspect drug caused the adverse event.

**MedDRA terms for liver failure include: Hepatic failure and associated disorders (HLT), Hepatic fibrosis and cirrhosis (HLT), Hepatic necrosis (PT), Hepatitis fulminant (PT), and Liver transplant (PT).

***MedDRA terms for liver toxicity include: Hepatic and hepatobiliary disorders (HLGT), Hepatobiliary investigations (HLGT), and Liver transplant (PT).

Key Findings: AERS Review of hepatotoxicity, 1998 – July 2001*

- 307 cases of liver injury were reported in the U.S., excluding suicides:
  - 60% had severe life-threatening liver injury and liver failure
  - 40% fatality
  - Among the cases that reported a dose (N=134), higher than recommended doses occurred more often than recommended or lower doses.

*Karwoski C. Briefing Document: Acetaminophen Containing Products and Hepatotoxicity. Division of Drug Risk Evaluation. August 2, 2002.
†Excluding an unspecified APAP product

Key Findings: AERS Review of hepatotoxicity*

- Adult cases [≥12 yrs] (n=282)
  - Daily doses of those that reported (N=124):
    - Mean 6.5 grams/day, Median 5 grams/day
    - Median daily dose increased with the severity of hepatic injury
    - 41% reported >4 grams/day
  - Acetaminophen/narcotic combinations were the most commonly implicated product†
  - ~25% reported the use of more than one acetaminophen product

*Karwoski C. Briefing Document: Acetaminophen Containing Products and Hepatotoxicity. Division of Drug Risk Evaluation. August 2, 2002.
†Excluding an unspecified APAP product

Key Findings: AERS Review of hepatotoxicity* [Cont]

- Pediatric cases [<12 yrs] (n=25)
  - 84% involved medication errors (use of improper measuring device, misinterpretation of labeling guidelines or instructions given by a health care practitioner, and confusion over product concentrations)
  - Most reported the use of only one acetaminophen product
  - OTC Single ingredient acetaminophen was the most commonly implicated product†

*Karwoski C. Briefing Document: Acetaminophen Containing Products and Hepatotoxicity. Division of Drug Risk Evaluation. August 2, 2002.
†Excluding an unspecified APAP product

AERS Case
Unintentional Overdose and Death, 2006

- 13 y.o. female took two acetaminophen containing meds x 5 days
  - Acetaminophen and Acetaminophen/Pseudoephedrine
  - Indications: URI and minor pain
  - Estimated acetaminophen dose was 6-7 gm/day

- Medical history
  - No history of self-harm and denied intentional self-harm
  - Denied exposure to potentially hepatotoxic substances
  - PMH – status-post kidney transplant & CMV
    - Concomitant meds: mycophenolate and tacrolimus

- Clinical
  - Labs: AST 10,068 and ALT 7,724, Bilirubin 4.1, INR 6.1, Acetaminophen level 74.6 mcg/mL
  - Encephalopathy, renal dysfunction (SrCr 4.1, BUN 47)
  - Treated with N-acetylcysteine
  - On liver transplant list but died prior to receiving a transplant

AERS Case of Unintentional Overdose in an Institutional Setting, 2001

- 33 yo female in a hospital being treated for CAP
- Developed abnormal liver labs
  - Elevated transaminases, LDH, and Alkaline phosphatase
  - Lab and serology tests were negative for other etiologies
- Review of her medication profile revealed several active concurrent acetaminophen products
  - Acetaminophen
  - Oxycodone/Acetaminophen
  - Propoxyphene/Acetaminophen
- Patient was unintentionally administered 1.3-6.2 gm/day
- All acetaminophen containing products were discontinued and her transaminases returned to normal

AERS Case of Unintentional Overdose from Lack of Pain Relief, 2002

- 33 yo male with an impacted wisdom tooth
- Self-treated with ibuprofen 200mg without relief
- Switched to extra strength acetaminophen (500mg/tab)
  - 1-2 tabs every 1-2 hrs x2 days
  - then increased the dose to 2-4 tabs every 1-2 hrs x1 day
  - consumed over 12 gms/24 hrs
- Presented to ED with pain, nausea, and malaise
  - APAP level 2.7 (units not reported)
  - LFTs normal
- Treated with activated charcoal and N-acetylcysteine
- Discharged after 3 days

AERS Limitations

- Extensive underreporting
- Lack of denominator data
- Quality of reports is variable
- Causality of drug-event association often in question
- Reporting biases

Summary of Findings

Emergency Department Visits (NHAMCS) and Hospitalizations (NHDS) (Objective 1):

- 51.6% of ED visits classified as unintentional, 41.7% as intentional, and 2.4% as undetermined.
- No decrease in the rate of hospitalizations due to intentional or unintentional overdoses despite the launch of the 2004 educational campaign.

Summary of Findings - 2

National Poison Data System (Objective 2):

- Acetaminophen-associated fatalities represent nearly 20% of all fatalities reported to NPDS and about 20% of these were unintentional.
- Among unintentional fatalities, in 5% of cases, two acetaminophen products were taken concomitantly.

Summary of Findings - 3

Adverse Event Reporting System (Objective 3):

- Acetaminophen continues to be the number one drug associated with reports of liver failure in the US according to crude AERS data.
- AERS continues to receive reports of liver toxicity and death associated with acetaminophen.

Single-Ingredient Acetaminophen Dose-Response Data in Adults

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Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products

Outline of Presentation

Dose-response efficacy information for:

- 1000 mg vs. 650 mg
  - NDA 17-053, 500 mg acetaminophen capsule (episiotomy)
  - Literature (analgesia)
- 1000 mg vs. 500 mg
  - Literature (analgesia and antipyresis)
- Meta-analyses (Cochrane reviews) on acetaminophen for postoperative pain
- Meta-analysis (Cochrane review) osteoarthritis studies
  1000 mg 4 times/day vs. placebo or vs. NSAIDs
  1000 mg 3 times/day vs. placebo or vs. ibuprofen
  650 mg 4 times/day vs. naproxen

Background

1953 NDA 08-717 (acetaminophen tablet)
1955 NDA 09-927 (Tylenol elixir)
1960 NDA 11-630 (Tylenol tablet)
1974 NDA 17-053 (Tylenol extra strength capsule)*
1975 NDA 17-552 (Tylenol extra strength tablet)
1994 NDA 19-872 (Tylenol arthritis pain)

* Only NDA with dose-response information

By 1972 (OTC Advisory Review Panel), acetaminophen was already established for OTC use:

Temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache

- For the minor pain of arthritis
- For the pain of menstrual cramps
- For the reduction of fever

Adult oral dosage is 325 mg to 650 mg every 4 hours while symptoms persist, not to exceed 3900 mg in 24 hours for not more than 10 days

Data on 1000 mg vs. 650 mg (NDA and literature)

FDA Documents: 500 mg Acetaminophen (1)

1974 approval NDA 17-053 (capsule) based on dose-response data:

500 mg acetaminophen (given as a 1000 mg dose) provides additional analgesic effectiveness compared to 325 mg (given as a 650 mg dose)

338 post-partum patients with episiotomy pain enrolled in 4 single-dose, double-blind, placebo-controlled, randomized studies to compare

- 1000 mg acetaminophen (taken as 500 mg capsule x 2)
- 650 mg acetaminophen (taken as 325 mg capsule x 2)

FDA documents: 500 mg acetaminophen (2)

1974 approval of NDA 17-053 (capsule) based on:

study	Subject #	Result: Change in pain intensity from baseline
1	25 per arm	1000 mg vs. 650 mg, $p < 0.05$ 1000 mg vs. placebo, $p < 0.01$ 650 mg vs. placebo, $p < 0.01$
2	50 per arm	1000 mg vs. 650 mg, $p < 0.01$ 1000 mg vs. placebo, $p < 0.01$ 650 mg vs. placebo, $p < 0.01$
3	12 vs. 13 vs. 13	No separate statistical analysis done due to small sample size Reviewer comment: **both active drugs significantly superior over placebo, but there was no difference between two APAP doses**
4	25 per arm	Inadequate assay sensitivity; **no difference between both active treatments and placebo**

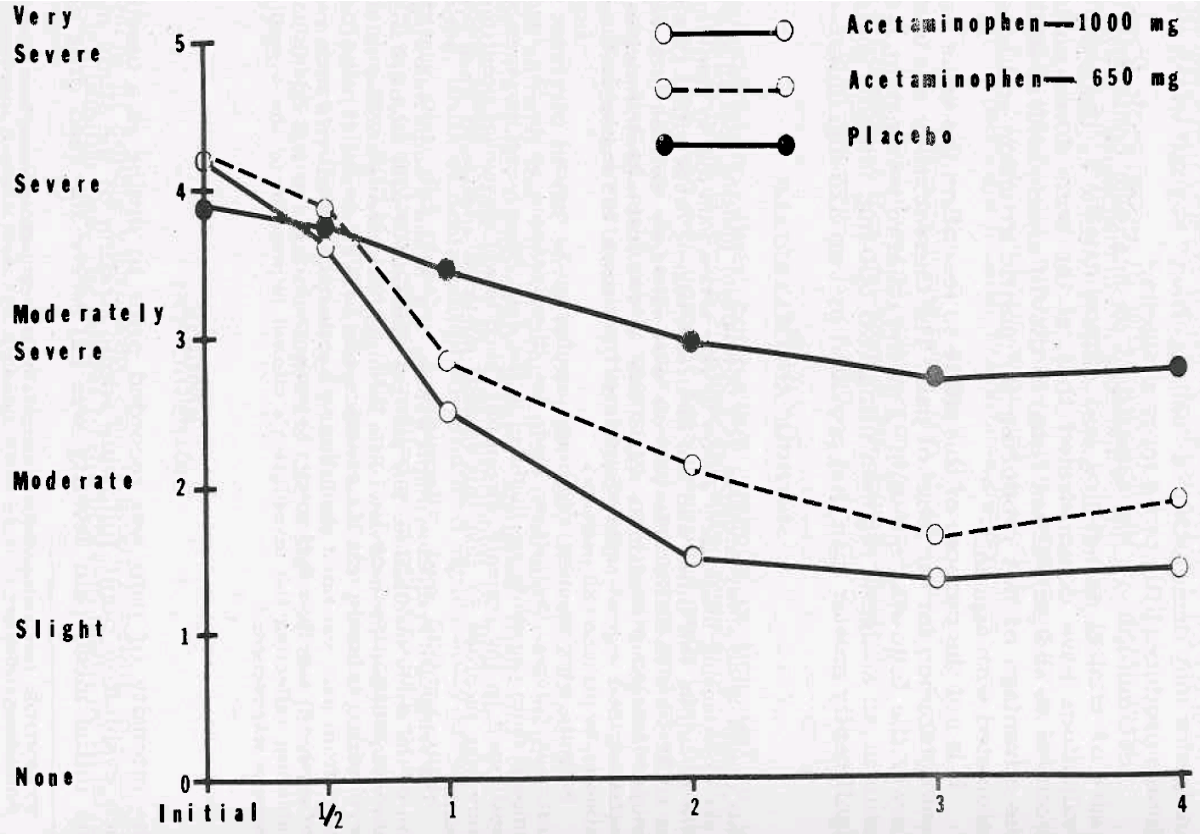
* Studies 1,2, and 3 later combined into one publication as Hopkinson et al, 1974

Literature: Analgesia 1000 mg vs. 650 mg

Study	Design	Treatment (acetaminophen subject N)	Pain model used	Result
Hopkinson 1974	SD, PC, DB, R	650 mg (88) 1000 mg (87) Placebo (88)	Episiotomy pain assessed over 4 hrs; 6-point pain scale	**1000 mg statistically significantly superior to 650 mg** for: Reduction of pain intensity ($p < 0.01$) Pain relief ($p < 0.01$) **650 mg statistically significantly superior to placebo** for: reduction of pain intensity ($p < 0.01$) Pain relief ($p < 0.01$)
Yuan 1998	SD, PC, DB, R, crossover	325 mg (18) 650 mg (18) 1000 mg (18) Placebo (18)	cold-induced pain over 180 seconds; 10-point pain scale	**Difference between 1000 mg and 650 mg not statistically significant** for: Pain intensity and “pain bothersomeness”

SD: single-dose; PC: placebo-controlled; DB: double-blind; R : randomized

Analgesia 1000 mg vs. 650 mg



Hopkinson 1974: pain intensity over time
(from NDA 17-053 resubmission studies 1-3; study 4 excluded.)

Summary: Direct Comparison 1000 mg (500 mg x 2) vs. 650 mg (325 mg x 2)

- Hopkinson
  - Advantage of 1000 mg over 650 mg
  - Used data from NDA 17-053, studies 1 to 3 (publication excluded study 4, a negative study)

- Yuan
  - Thermal cold-induced pain, not OTC pain model
  - no difference between the two doses

- There are dose-response data for severe episiotomy pain (studies 1 & 2 for NDA 17-053/Hopkinson)
- No published comparison on mild to moderate pain
- Unclear data from severe pain in this selected population would be applicable to mild to moderate pain (OTC indications)

Data on 1000 mg vs. 500 mg (literature)

Analgesia 1000 mg vs. 500 mg

Study	Design	Treatment (acetaminophen N)	Pain model used	Result
Quiding 1984	2-dose, AC, DB, R	500 mg (30) 1000 mg (29) Codeine 60 mg	Post-op pain (3rd molar removal) assessed over 10 hrs after 1st dose	**1000 mg statistically significantly superior to 500 mg** Pain reduction
McQuay 1986	SD, AC, DB, R	500 mg (30) 1000 mg (30) Ketoprofen 5 mg Ketoprofen 10 mg Ketoprofen 20 mg	Post-op pain (orthopedic) assessed over 10 hrs	**1000 mg statistically significantly superior to 500 mg** SPID (summed pain intensity)
Nystrom 1988	2-dose, DB, R	500 mg x 2 (41) 1000 mg x 2 (41) Diflunisal 500 mg x 1 & acetaminophen 500 mg rescue	Post-op pain (removal of 2 wisdom teeth) assessed over 10 hrs after 1st dose	**1000 mg statistically significantly superior to 500 mg** Pain reduction 10-hr SPID Duration of effect
Seymour 1996	SD, PC, DB, R	500 mg (41) 1000 mg (41) Ketoprofen 12.5 mg Ketoprofen 25 mg placebo	Post-op pain (3rd molar removal) assessed over 6 hrs)	**No statistically significant differences between two acetaminophen doses** **All treatments effective vs. placebo ($p < 0.01$)**

Antipyresis 1000 mg vs. 500 mg

Study	Design	Treatment (acetaminophen subject N)	Subjects	Result (4 hours)
Bachert 2005	SD, PC, DB, R	Acetaminophen 500 mg (79) Acetaminophen 1000 mg (79) ASA 500 mg ASA 1000 mg Placebo	Adult patients with URI symptoms and acute fever 38.5˚C-40.0˚C	**500 mg vs. placebo** **Mean reduction 1.25˚C (p < 0.001)** **1000 mg vs. placebo** **Mean reduction 1.71˚C (p < 0.001)** **1000 mg vs. 500 mg (p < 0.001)** **Headache, achiness, feverish discomfort reduced equally by the two acetaminophen doses (p < 0.001) at most time points**

Summary: Direct Comparison 1000 mg (500 mg x 2) vs. 500 mg

- Analgesia (4 reports)
  - All used appropriate pain models.
  - The only placebo-controlled study (Seymour 1996) showed no statistical difference between efficacy of the two doses.
- Antipyresis (1 report)
  - Both 500 mg and 1000 mg doses are effective.
  - Additional fever reduction from 1000 mg was ~0.5˚C.

Meta-analyses

3 Cochrane reviews on analgesic efficacy

63 randomized, double-blind studies

Overall, acetaminophen is effective in providing analgesia for postoperative pain.

- Based on cross-study comparisons
- Based on "number needed to treat" (NNT)
- Lower NNT indicates better efficacy

NNT = 1/ [(proportion treatment group with 50% relief) – (proportion placebo group with 50% relief)]

Cochrane Reviews: Acetaminophen for Postoperative Pain

	Indication	Study design	# studies	# subjects	NNTs by dose vs. placebo
1	Single dose, with and without codeine, for postoperative pain	DB, R	•40 acetaminophen vs. placebo •22 acetaminophen + codeine vs. placebo •12 acetaminophen + codeine vs. acetaminophen alone	N = 4171 N = 1407 N = 794	500 mg = 5.6 600/650 mg = 5.3 1000 mg = 4.6 600/650 mg + codeine = 3.6
2	Pain relief after removal of wisdom teeth	R, PC, DB, PG	21	N = 1148 acetaminophen N = 892 placebo	<1000 mg = 4 at 4 hours 1000 mg = 3 at 4 hours <1000 mg = 6 at 6 hours 1000 mg = 5 at 6 hours
3	Single dose for postoperative pain (update of study 1)	R, PC, DB	47	N = 2561 acetaminophen N = 1625 placebo	500 mg = 3.5 600/650 mg = 4.6 975/1000 mg = 3.8

R: randomized; DB: double-blind, PC: placebo-controlled; PG: parallel group
NNT: number needed to treat for one patient to achieve 50% pain relief over 4-6 hours
None of the three reviews had definite dose-response findings. All NNT 95% CI overlap.

Summary: Postoperative Pain from Cochrane Reviews

- Acetaminophen at all doses studied is effective for acute postoperative pain after procedures.

- No dose is significantly more effective than any other.

Acetaminophen Use in Osteoarthritis

- American College of Rheumatology Recommendations for the medical management of osteoarthritis of the hip and knee (2000): Acetaminophen "merits a trial as initial therapy, based on its overall cost, efficacy, and toxicity profile…The daily dose of acetaminophen should not exceed 4 gm."

- Cochrane review (acetaminophen for osteoarthritis):
  - 12 studies used 4000 mg/d (6 vs. placebo, 10 vs. NSAIDs)
  - 2 studies used 3000 mg/d (1 vs. placebo, 1 vs. ibuprofen 1200 mg/d)
  - 1 study used 2600 mg/d (vs. naproxen 650 mg/d)

2006 Cochrane Review: Acetaminophen for Osteoarthritis

Studies	Study design	Treatment (# subject)	Outcome measures	Result
12 studies 1000 mg 4 times per day 7 days to 12 weeks OA knee or hip	R, DB	6 acetaminophen vs. placebo 10 acetaminophen vs. NSAIDs total N = 5526	Pain intensity Functional disability	4 PC studies showed better efficacy of acetaminophen over placebo but 2 PC studies did not NSAIDs had better pain reduction results
Williams 1993 650 mg 4 times per day x 2 yrs OA of the knee	R, DB, PG	Acetaminophen (88) Naproxen 375 mg b.i.d. (90)	Radiographic progression Withdrawal due to lack of efficacy	2 yr drop-out rate 69.3% (vs. 61.1%) Improvement from baseline at 6 weeks: **pain on motion (p = 0022)** **physician global assessment (p = 0.003)**
Zoppi 1995 1000 mg 3 times per day x 7 days OA knee or hip	R, DB, PC, PG	Acetaminophen (30) Placebo (30)	Pain intensity Patient assessment Desire to continue drug	**SPID** (VAS daily pain scores) $p < 0.05$ **Desire to continue** 64% (vs. 37%, $p < 0.05$)
Boureau 2003 1000 mg 3 times per day x 14 days OA knee or hip	R, DB, PG	Acetaminophen (111) Ibuprofen 400 mg t.i.d. (111)	Pain intensity Functional disability Patient global assessment	**Improvement in stiffness, pain, physical function** **WOMAC scores** improved for both groups but ibuprofen significantly better (p = 0.002)

R: randomized; DB: double-blind, PC: placebo-controlled; PG: parallel group

Summary: Osteoarthritis Studies

- 4000 mg/d acetaminophen
  - More data for support
- 3000 mg/d acetaminophen
  - Efficacy demonstrated in placebo-controlled trial (Zoppi)
  - Improvement in stiffness, pain & physical function (Boureau)
- 2600 mg/d acetaminophen (Williams)
  - significant improvement at 6 weeks for pain on motion and physician global assessment

- No published data directly comparing acetaminophen doses in osteoarthritis

Overall Summary on Efficacy

- Limited data to support advantage of 1000 mg acetaminophen over 650 mg (severe episiotomy pain only)
- Unclear if 1000 mg better than 650 mg for mild to moderate pain
- No placebo-controlled studies to show advantage of 1000 mg over 500 mg
- Some data supporting effectiveness of 2600 mg to 3000 mg/day acetaminophen for osteoarthritis symptom relief

Maximum OTC acetaminophen dosage is identical to maximum Rx dosage

Drug	Maximum daily recommended dose (mg/day)	
	Prescription	OTC
Acetaminophen	4000	4000
Ibuprofen	3200	1200
Naproxen	1000	600
Naproxen sodium	1100	660
ketoprofen	300	75

Risk/Benefit Considerations

- 1974 approval decision 500 mg formulation (1000 mg dose): clinical trials raised no safety issues
- Unlike other OTC analgesics, maximum daily dose identical for OTC and Rx
- Narrow safety margin of acetaminophen
- Would lowering OTC dose (single/daily) improve safety without compromising efficacy?
- Unintended consequences of dose reduction?

Rx Acetaminophen Combination Products

Jane Filie, M.D.
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Division of Analgesia, Anesthesia and Rheumatology Products
June 29, 2009

Overview

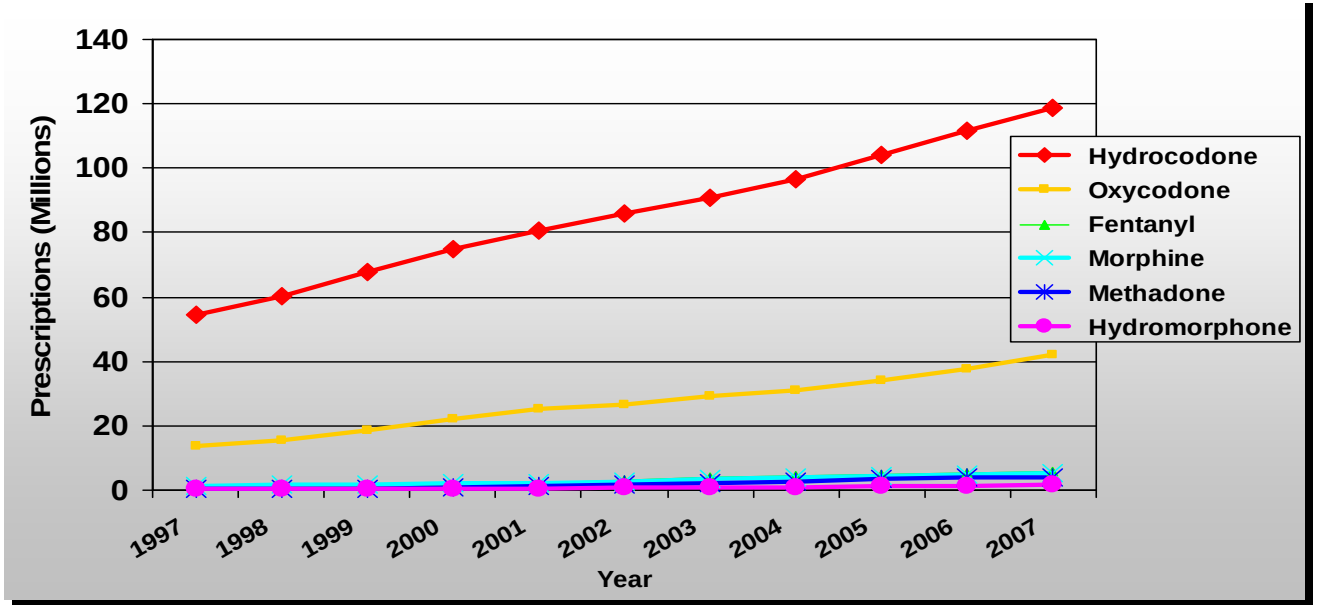
- Pain management in the US
- DEA Regulations
- Options for improving the safety of the Rx acetaminophen combination products:
  - Unit of use packaging
  - Improve prominence of “acetaminophen” on the label
  - Med Guide
  - Lowering the dose in combinations
  - Unbundling of narcotic combinations
- Alternatives for pain management and associated risks

Pain management in the US

- Under-treatment of pain remains a major public health problem.
- 50 million Americans are partly or totally disabled due to pain and these numbers are expected to rise as the population ages.
- Treatment usually begins with non-opioid analgesics, next opioid/non-opioid combinations, then single entity opioid analgesics.

Prescription Data: Total Retail Prescriptions Dispensed For Selected Opioids, Years 1997-2007

SDI Vector One™: National (VONA). Extracted 3/2008



- Hydrocodone combination products #1 among all dispensed prescriptions for past 10 years
  - nearly 120 million Rx in 2007
- Oxycodone products - 42 million Rx in 2007

DEA Regulations

- The Controlled Substances Act (CSA) was enacted in 1970 and provides the DEA with authority to regulate the manufacture and distribution of narcotics, stimulants, depressants, hallucinogens, anabolic steroids, and chemicals used in the illicit production of controlled substances.
- There are 5 schedules under the CSA, Schedule I (highest abuse potential) to V (least abuse potential).
- Schedules II to V have approved medical uses.

Controlled Substance Act

- Schedule III (codeine and hydrocodone combinations)
  - Potential for abuse is less than schedule II.
  - Hydrocodone, up to 15 mg/dosage unit, in combination with non-narcotic can be a schedule III drug.
  - Dispensing of these drugs:
    - requires written or oral prescription.
    - may not be filled or refilled more than six months after the date of prescription.
    - may not be refilled more than five times after the date of prescription.

Controlled Substances Act

- Schedule II (single agents codeine, fentanyl, morphine, oxycodone)
  - These drugs have a high potential for abuse.
  - Hydrocodone alone is a schedule II drug.
  - Dispensing of these drugs:
    - requires written prescription each month to the pharmacy.
    - may not be refilled.

Combination Rx products containing Acetaminophen

Acetaminophen +

- codeine
- hydrocodone
- oxycodone
- pentazocine
- propoxyphene
- tramadol

Options to improve the safety of the prescription acetaminophen products

- Unit of use packaging
- Improve prominence of “acetaminophen” on the label
- Medication Guide
- Lowering the dose in combinations
- Discontinuing narcotic/acetaminophen combinations

Unit of use packaging

- *Unit of use packaging* means that the product is packaged by industry and shipped to the pharmacy ready for sale, without having to be repackaged.
- This would not necessarily restrict the number of dosage units available in the container.

Unit of use packaging

- This proposal would improve the safe use of this product by:
  - standardizing the information on the prescription label (i.e., “acetaminophen” instead of “APAP”, liver warning).
  - providing appropriate risk information through more reliable delivery of a MedGuide.

Improve prominence of "acetaminophen" on the label

- When products are repackaged at the pharmacy, ingredient names can be abbreviated on labels, e.g. APAP in place of acetaminophen.
- Consistent use of the full word, acetaminophen, on prescription labels can be achieved via unit-of-use packaging.

Medication Guide

- 21 CFR Part 208—MEDICATION GUIDES FOR PRESCRIPTION DRUG PRODUCTS
- Patient labeling for human prescription drug products… that the FDA determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information.

Medication Guide

- Difficult to ensure delivery of Medication Guides to patients when products are repackaged at the pharmacy.
- Delivery can be improved via unit-of-use packaging.
- Challenge remains in ensuring patients read and understand the information.

Lowering the Acetaminophen Dose in Combinations

- Wide range of amounts of acetaminophen doses in combination products, from 250 mg to 750 mg, 500 mg most common in prescribed in these combination products.
- Little data to support value of using products with 500 mg (1000 mg dose) over products with 325 mg (650 mg dose).

Discontinuation of Opioid/Acetaminophen Combinations

- Fewer than half of the cases of acute liver failure due to acetaminophen are associated with prescription acetaminophen combination products.
- One must consider the overall risk and benefit of the alternatives that will replace the acetaminophen/opioid combination products.

Discontinuation of Opioid/Acetaminophen Combinations

- Patients who need combination acetaminophen and opioid drugs may be unable to obtain relief with NSAIDs or unable to tolerate them.
- Patients who receive the opioid combination products have been deemed not to need single agent opioids by their prescribers.

Discontinuation of Opioid/Acetaminophen Combinations

- Hydrocodone is not currently available as an approved single agent product.
- Availability would require submission and review of a new drug application.
- Hydrocodone alone is a schedule II drug which has more restrictions for the prescribers and patients.

Alternatives to Acetaminophen/Opioid Combinations

- Ibuprofen, naproxen, diclofenac, celecoxib
- Hydrocodone/acetaminophen, oxycodone/acetaminophen, codeine/acetaminophen
- Single entity oxycodone, hydromorphone

Diagnoses associated with use
SDI, Physician Drug and Diagnosis Audit™

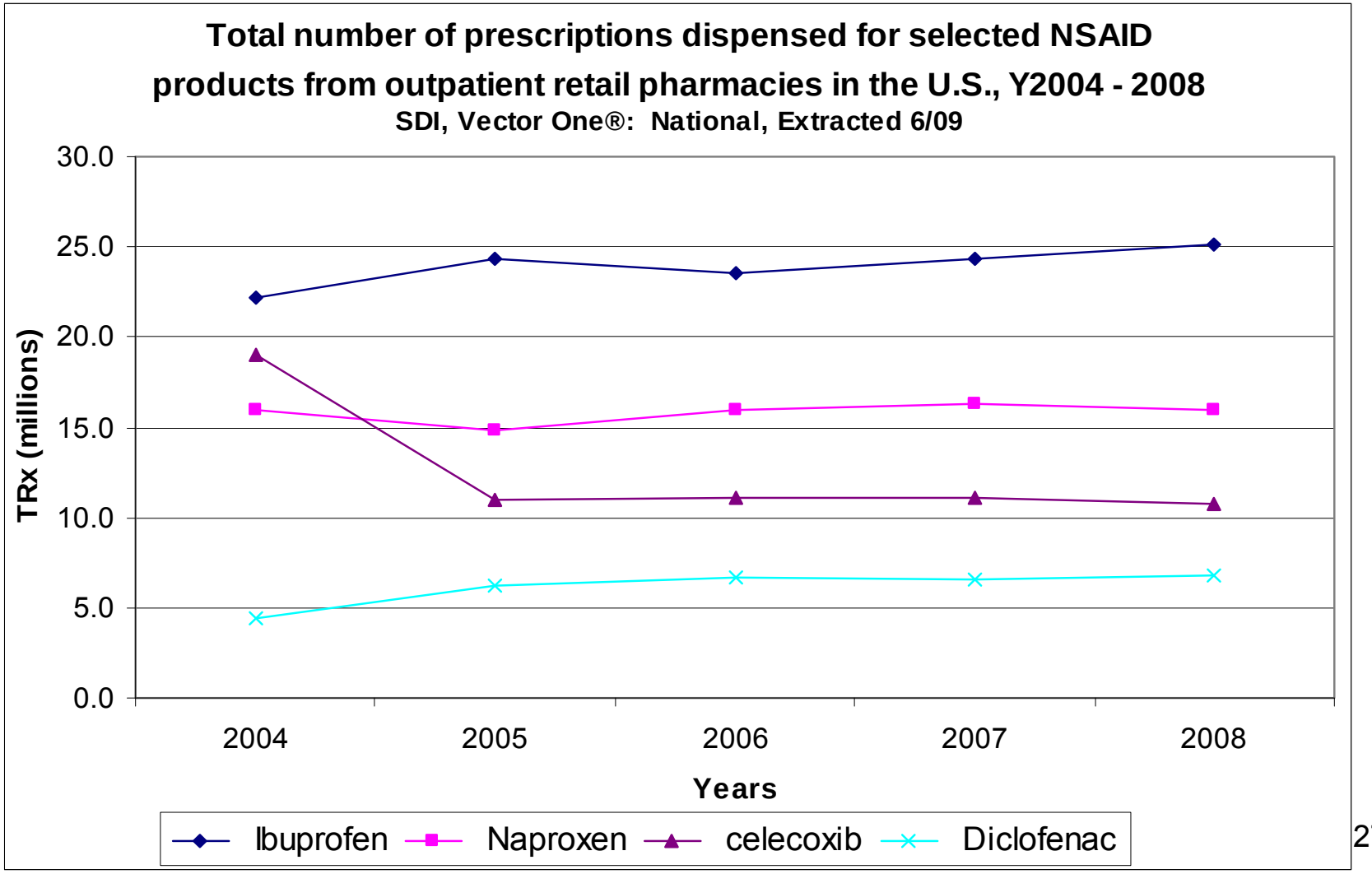
The two most common diagnostic codes:

- Diseases of the Musculoskeletal System & Connective Tissue (710-739)
- Fractures, Sprains, Contusions, Injuries (800-999)

NSAIDs

- Well known adverse event profile:
  - GI ulcers, bleeding, perforation
  - cardiovascular thrombotic events
  - sodium and fluid retention, congestive heart failure
  - acute renal failure
  - hepatotoxicity
  - bronchospasm

Prescription Data: Total Retail Prescriptions Dispensed For Selected NSAIDs



NSAID-Induced Gastropathy: Morbidity and Mortality in the US

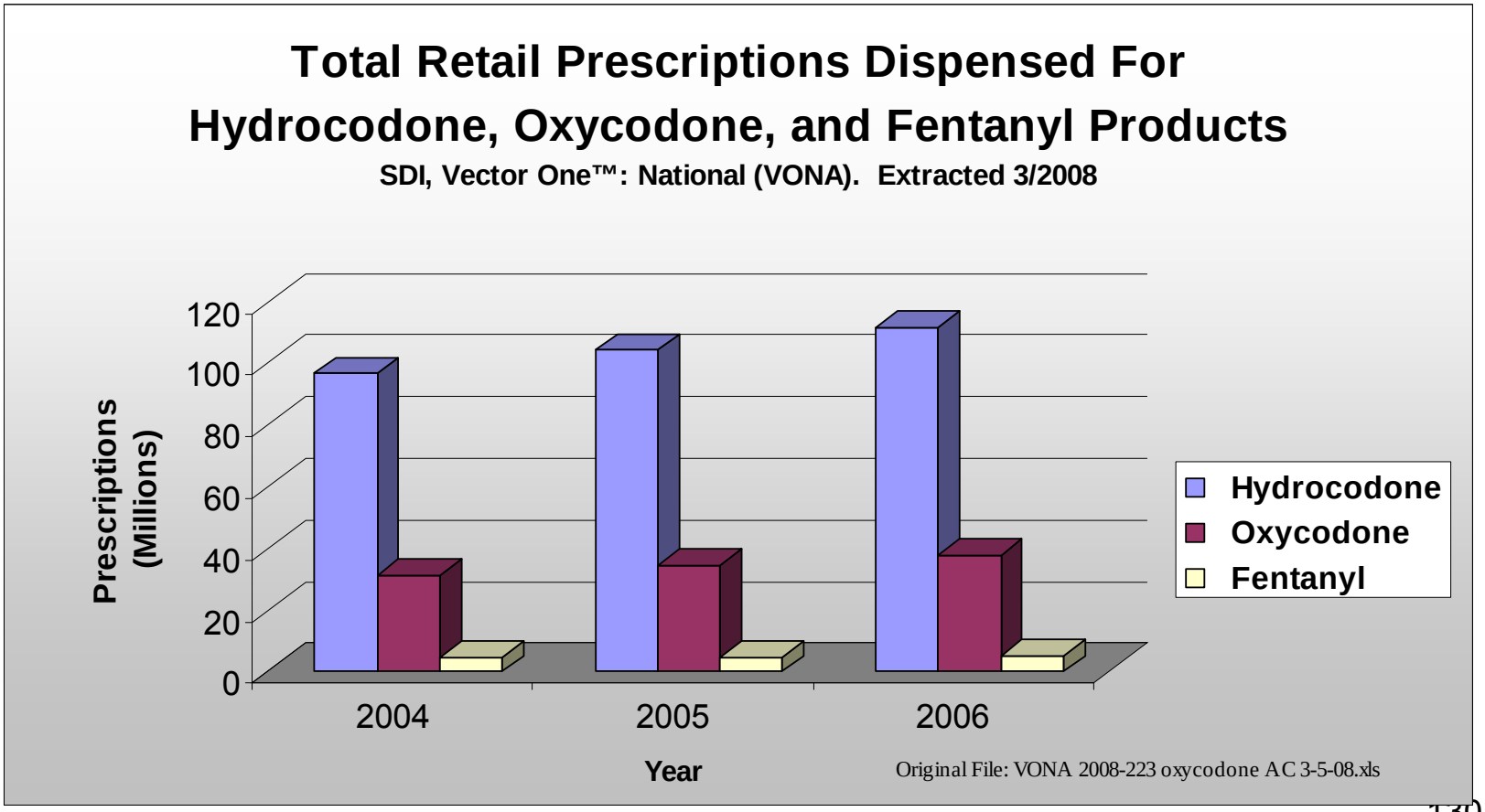
- Estimated total hospitalizations for serious GI complications: 32,000 per year.
- Estimated number of NSAID-related deaths vary in the literature, may be 3,200 per year or more.
- The replacement of the combination products for NSAIDs would not be expected to reduce the overall morbidity associated with acetaminophen/opioid combination products.

Schedule II Opioids

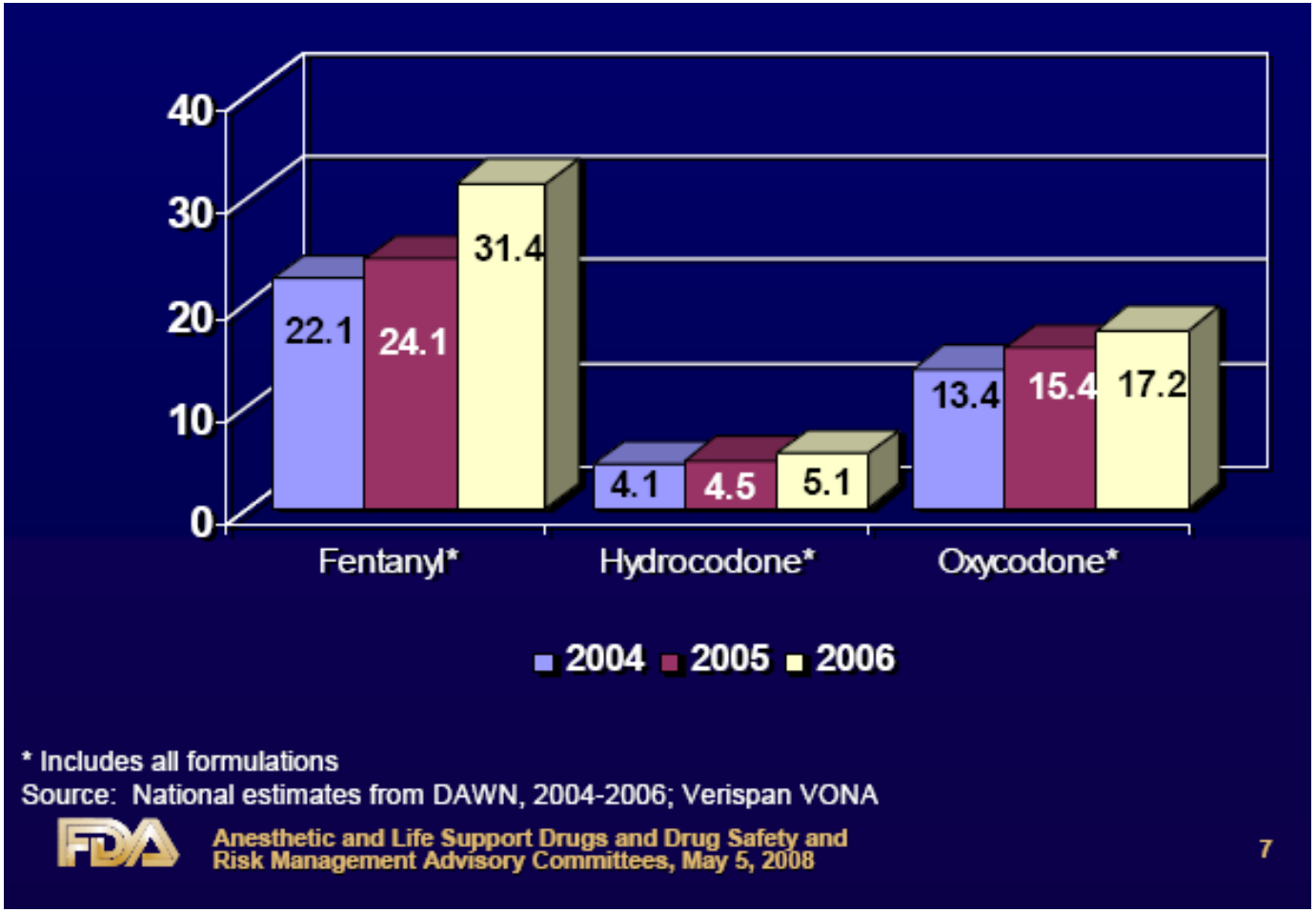
- These include oxycodone, hydromorphone, morphine.
- Well known adverse events:
  - somnolence
  - nausea, vomiting, constipation
  - urinary retention
  - histamine release (urticaria, pruritus, exacerbation of asthma)
  - respiratory depression
  - addiction, misuse and abuse

Projected Retail Prescriptions Dispensed for Selected Opioids, 2004-2006

SDI, Vector One™: National (VONA). Extracted 3/2008



DAWN: ED Visits -- Non-Medical Use per 10,000 Retail Prescriptions 2004 – 2006



* Includes all formulations

Source: National estimates from DAWN, 2004-2006; Verispan VONA

Schedule II Opioids

- It is unclear the reason for the differences in the DAWN data for hydrocodone and the other opioids.
  - The amount of hydrocodone in the combination products (limited by the provisions of the CSA for a Schedule III product) may result in fewer emergency department visits.
  - The presence of acetaminophen may make this less appealing for misuse.
- Substitution of the single entity Schedule II opioids for acetaminophen/hydrocodone combination products could result in a rise in cases of misuse and abuse.

Summary

- The acetaminophen/hydrocodone combination products are the most widely prescribed drugs for the treatment of pain.
- Improved safety of the combination products may be achieved with improved labeling, patient information and limiting of the amount of acetaminophen in combination products.
- Elimination of the acetaminophen/hydrocodone combination products may not necessarily result in an overall reduction in risk due to the risks associated with available analgesic alternatives.

FDA Consumer Education on the Safe Use of Acetaminophen

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(301)796-3121

Education Campaign History

- January 2004 – FDA launched the "Safe Use of Over-the-Counter Pain Relievers and Fever Reducers" Campaign.

- Education Messages covered both acetaminophen and NSAIDs

2004 Products

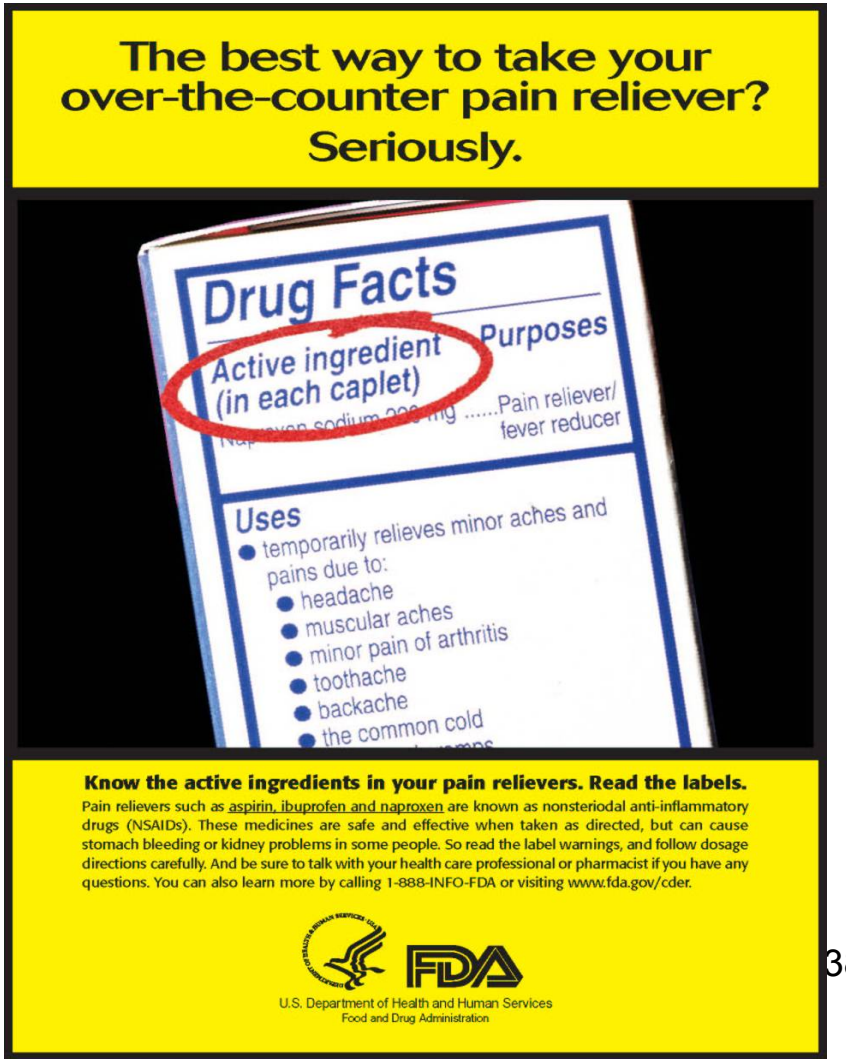
- Brochure – English and Spanish
- Print Public Service Announcements (2)
- FDA Consumer Magazine Story
- Internet Banners
- Newspaper Story (NAPS)
- FDA Patient Safety News (Video)

English and Spanish Brochure

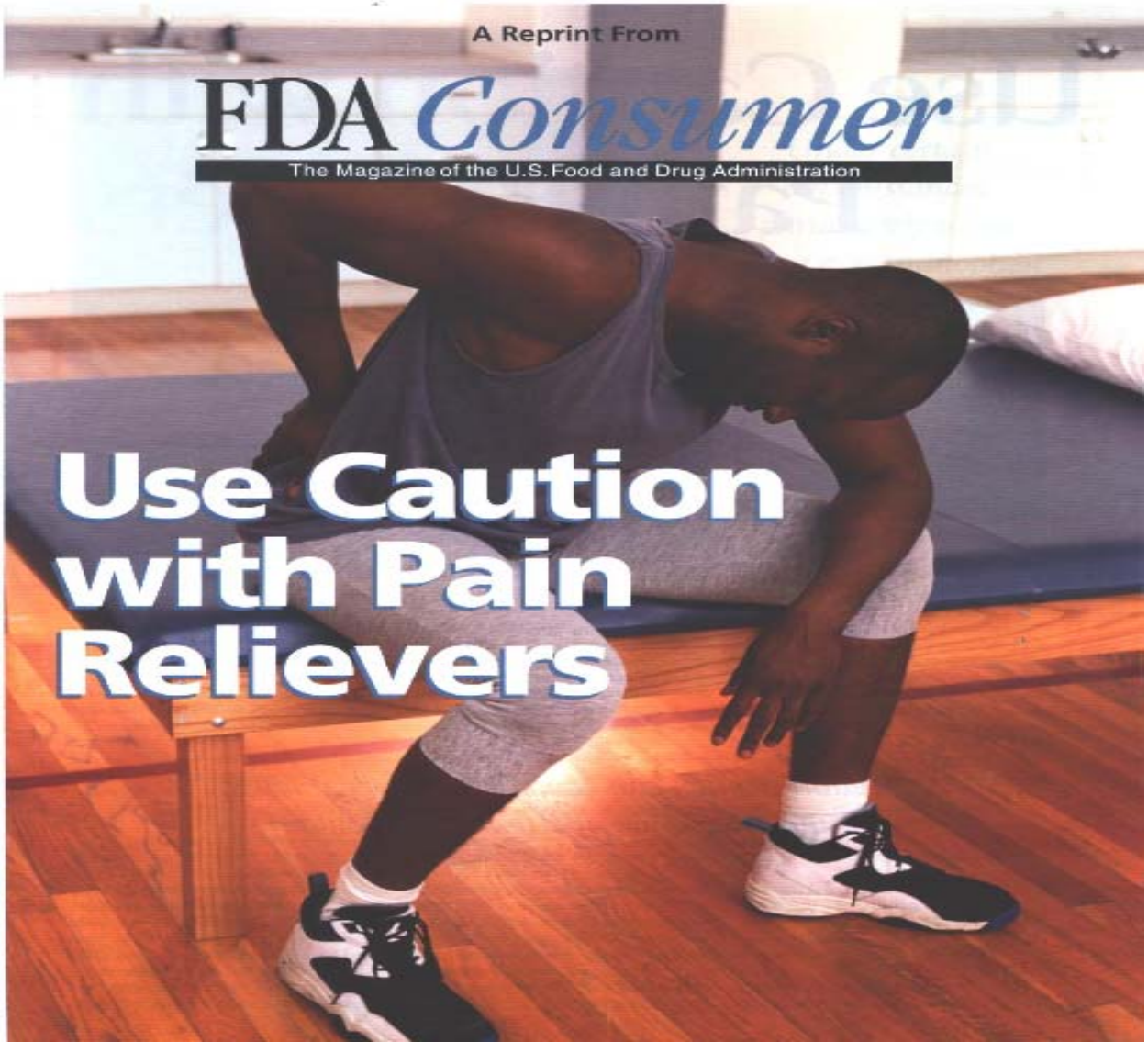
2004 Print Public Service Announcements

Acetaminophen

NSAIDs



FDA Consumer Magazine



2004 Newspaper Story

- 124 placements
- 5,895,648 readership

Health Hints

Use Caution With Pain Relievers

(NAPS)—Pain relievers, when used correctly, are safe and effective. Millions of people use these medicines every day. Not using them according to the label directions can have serious consequences.

The U.S. Food and Drug Administration (FDA) wants consumers to benefit from these medicines and not be hurt by them. You should know the active ingredients and directions of all your medicines before you use them.

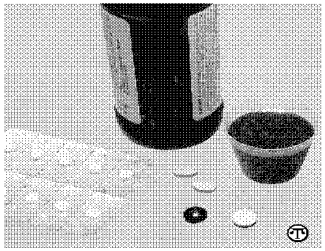
Over-the-counter (OTC) medicines list all their active ingredients on the package. For prescription drugs, the leaflet that comes with your prescription lists the active ingredients contained in the medicine.

Many OTC medicines sold for different uses have the same active ingredient. Also, active ingredients in OTC medicines can be ingredients in prescription medicines. For example, a cold-and-cough remedy may have the same active ingredient as a headache remedy or a prescription pain reliever.

There are basically two types of OTC pain relievers. Some contain acetaminophen and others contain non-steriodal anti-inflammatory drugs (NSAIDs). These medicines are used to relieve the minor aches and pains associated with headaches, colds, flu, arthritis, toothaches, and menstrual cramps.

These medicines are also used to treat migraine headaches, and to reduce fever.

Acetaminophen is a very common pain reliever and fever reducer. Taking too much of this active ingredient can lead to liver damage. The risk for liver damage may be increased if you drink three or more alcoholic drinks while using acetaminophen-containing medicines.



Careless use of acetaminophen can cause more pain.

NSAIDs are common pain relievers and fever reducers. Examples of OTC NSAIDs are aspirin, ibuprofen, naproxen sodium, and ketoprofen. Your risk for stomach bleeding may increase if you are over 60, taking prescription blood thinners, have previous stomach ulcers or other bleeding problems.

If you have any of these factors, you should talk to your doctor before using NSAIDS.

NSAIDs can also cause reversible damage to the kidneys. The risk of kidney damage may increase in people who are over 60, people who have high blood pressure, heart disease or pre-existing kidney disease, and people who are taking a diuretic.

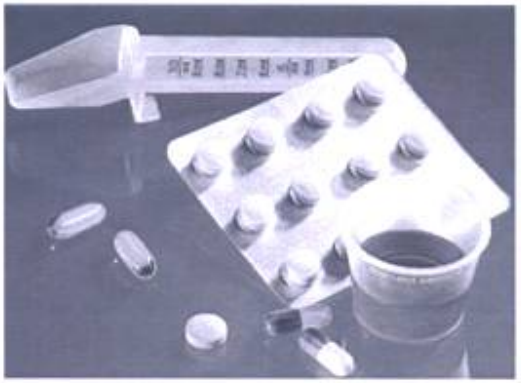
The FDA recommends that you talk with your healthcare professional if you have questions about using OTC medicine before using it in combination with other medicines—either OTC or prescription medicine.

You can learn more about what medicines are right for you by reading the label carefully and talking to your healthcare professional or pharmacist.

For more information, visit www.fda.gov or call 1-888-INFO-FDA.

Prescription leaflet

Why is it important to know that all these medicines contain acetaminophen?



ecause too much can damage your liver.

taminophen is an active ingredient found in more than 600 over-counter and prescription medicines, such as pain relievers, cough pressants and cold medications. It is safe and effective when used rectly, but taking too much can lead to liver damage. Different dicines contain different amounts, so follow dosage directions efully. And don't take more than one acetaminophen product a day hout first speaking to a health care professional.

Know the active ingredients in your medicines. Read the label.

More about acetaminophen and other over-the-counter pain relievers/fever reducers

What are pain relievers/fever reducers?
There are two categories of over-the-counter pain relievers/fever reducers: acetaminophen and nonsteriodal anti-inflammatory drugs (NSAIDs). Acetaminophen is used to relieve headaches, muscle aches and fever. It is also found in many other medicines' such as cough syrup and cold and sinus medicines. OTC NSAIDs are used to help relieve pain and reduce fever. NSAIDs include aspirin, naproxen, ketoprofen and ibuprofen, and are also found in many medicines taken for colds, sinus pressure and allergies.

How do I use pain relievers/fever reducers safely?
These products, when used occasionally and taken as directed, are safe and effective. Read the labels of all your over-the-counter medicines so you are aware of the correct recommended dosage. If a measuring tool is provided with your medicine, use it as directed.

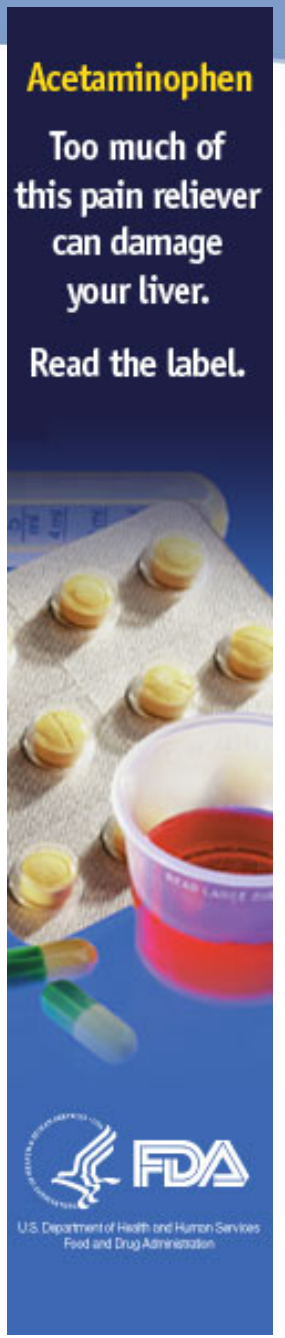
What can happen if I do not use pain relievers/fever reducers correctly?
Using too much acetaminophen can cause serious liver damage, which may not be noticed for several days. NSAIDs, for some people with certain medical problems, can lead to the development of stomach bleeding and kidney disease.

What if I need to take more than one medicine?
There are many OTC medicines that contain the same active ingredient. If you take several medicines that happen to contain the same active ingredient, for example a pain reliever along with a cough-cold-fever medicine, you might be taking two times the normal dose and not know it. So read the label and avoid taking multiple medicines that contain the same active ingredient or talk to your pharmacist or health care professional.

2004 Internet Banners

Placements

- WebMD
- HealthNewsDigest
- MayoClinic



Posted on Mayoclinic.com

FDA Patient Safety News Video

Please note that due to technical difficulties this video can not be shown please refer to the transcript

Radio Public Service Announcements 2007

"Acetaminophen – Read the Label"

A 20-second and 30-second spot

(Due to technical difficulties the service announcements will not be audible please refer to the transcript)

Acetaminophen – Read the Label 00:00:20316 KB PDF

Acetaminophen – Read the Label 00:00:30460 KB PDF

- Reached:

2007 Newspaper Article on Acetaminophen

- 236 placements
- 19,514,720 readership

Health Bulletin

Use Caution With Pain Relievers

(NAPS)—Acetaminophen is a safe and effective pain reliever that benefits millions of consumers. However, taking too much could lead to serious liver damage. There are about 600 products that contain acetaminophen, including cough and cold products and sleep aids. It is also an ingredient in many prescription pain relievers. The Food and Drug Administration warns consumers that all over-the-counter pain relievers should be taken with care to avoid serious problems that can occur with misuse.

Parents should be cautious when giving acetaminophen to children. For example, the infant drop formula is three times stronger than the children's suspension. To help make sure your infant is getting the infants' formula and your child is getting the children's formula, you should read and follow the directions on the label every time you use a medicine. Parents are cautioned against giving any acetaminophen or cough and cold medications to children under 2 years of age without the advice of a health care provider.

Avoid Overdosing

To avoid accidental overdosing, it's very important not to take more than the recommended dose on the label. Also, you should not take acetaminophen for more days than recommended, or take more than one drug product that contains acetaminophen at the same time. Consumers should be aware that taking more than the recommended dose will not provide more relief.

FDA

Always consult your doctor when you are taking more than one medication with acetaminophen.

Liver Damage

Your liver helps break down and remove many chemicals or drugs that enter your body. Too much acetaminophen overloads the liver's ability to process the drug safely. Under certain circumstances, particularly when more acetaminophen is ingested than is recommended on the label, more of the toxic chemical is produced than the body can easily eliminate, resulting in serious damage to the liver.

Signs of Liver Disease

The signs of liver disease include abnormally yellow skin and eyes, dark urine, light-colored stools, nausea, vomiting and loss of appetite. The signs can be similar to flu symptoms and may go unnoticed for several days if you believe your symptoms are related to a cold or flu you may already have. Serious cases of liver disease may lead to mental confusion, coma and death.

For more information, visit www.fda.gov or call 1-888-INFO-FDA.

"Medicines In My Home" Educational Program

Medicines In My Home

- Teachers' Room
- Students' Room
- Consumers' Room
- Press Room
- About Us
- Contact Us

Welcome to **Medicines in My Home**, an interactive and educational program about the safe and effective use of over-the-counter medicines. This program was developed by the Food and Drug Administration with Maryland's Montgomery County Public School system and in cooperation with the National Council On Patient Information and Education.

Medicines in My Home is growing and changing. You can receive an email notification when new materials are added.

Partnerships

- United Health Foundation
- National Council on Patient Information and Education
- National Consumers League
- Wellmark/Blue Cross Blue Shield
- New York State Dept. of Health

Reprinted the – brochure, print PSA (into a poster)
Disseminated to:

- NY retailers (4,000),
- hospitals (257),
- poison control centers (6),
- and each of NY county's Kidney Foundation, Liver Foundation, and Diabetes Association at no cost.

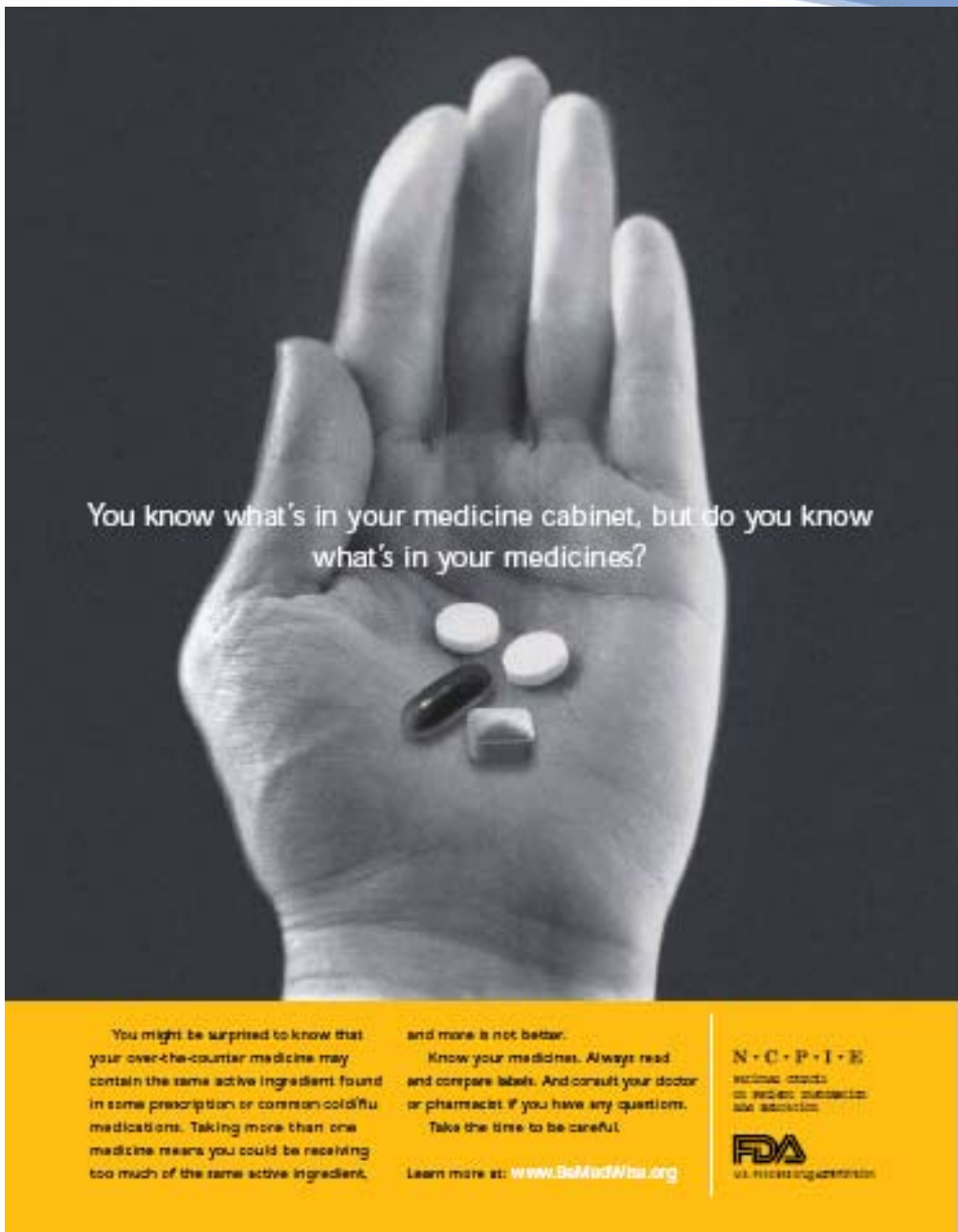
National Consumers League

Print PSA

National Council on Patient Information and Education

- TV advertisement on TNT networks in 2005
- Media tour (radio) in 2004
- Print public service announcement

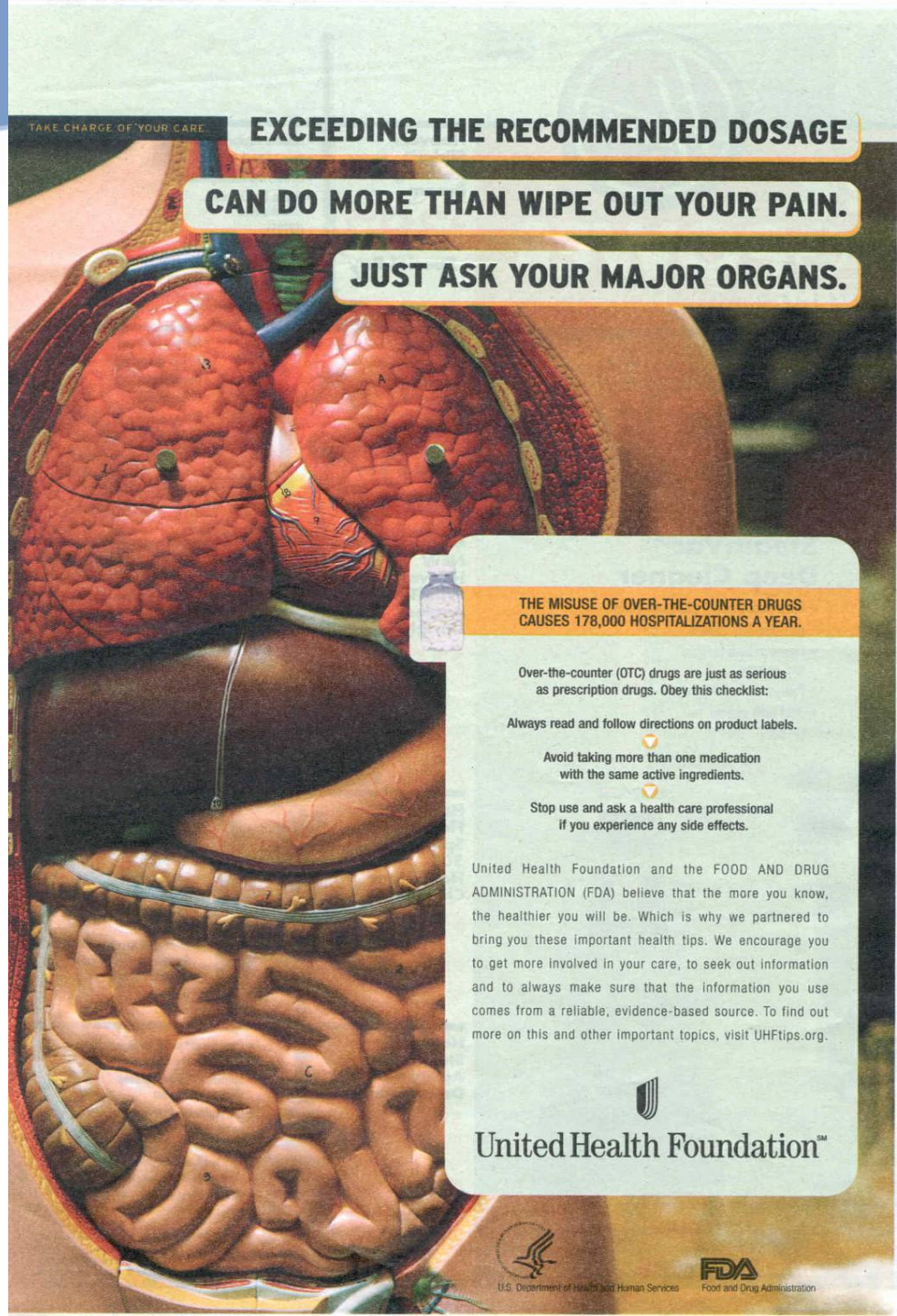
www.bemedwise.org



United Health Foundation

Print Media Outlets

Parade
People
Better Homes and Gardens
Family Circle
Ladies Home Journal
Prevention
Woman's Day
Ebony
Good Housekeeping
Reader's Digest
Parenting
WebMD
USA Weekend
MediZine



Consumer Education Materials 2009

- Brochure (using 2004 brochure)
- "Medicines In My Home" Web interactive program
- Q&As (written and podcast)
- FDA "Consumer Corner" video
- FDA "Patient Safety News" video
- FDA Consumer Health Updates
- Fact Sheets for:
  - Parents
  - Seniors
  - Young Adults (college age students)
- Posters for Health Clinics and College/University Health Centers
- In-store 30 sec.broadcast announcement
- Radio and Print Public Service announcements
- Newspaper article (NAPS)

Consumer Messages

Primary message:

Acetaminophen is generally a safe and effective drug as long as you:

- Read and follow the information given by your doctor and the medicine label
- Never use more than directed
- Never use more than 1 medicine containing acetaminophen at a time

Secondary messages:

Ask your doctor before using acetaminophen if you:

- Drink alcohol, 3 or more drinks every day
- Have liver disease
- Take warfarin, a blood thinning medicine

Patient Safety News (video) for Consumers

Please note that due to technical difficulties this video cannot be shown please refer to the transcript

Patient Safety News (video) for Health Care Professionals

Please note that due to technical difficulties this video cannot be shown. Please refer to the transcript

FDA Consumer Education Websites

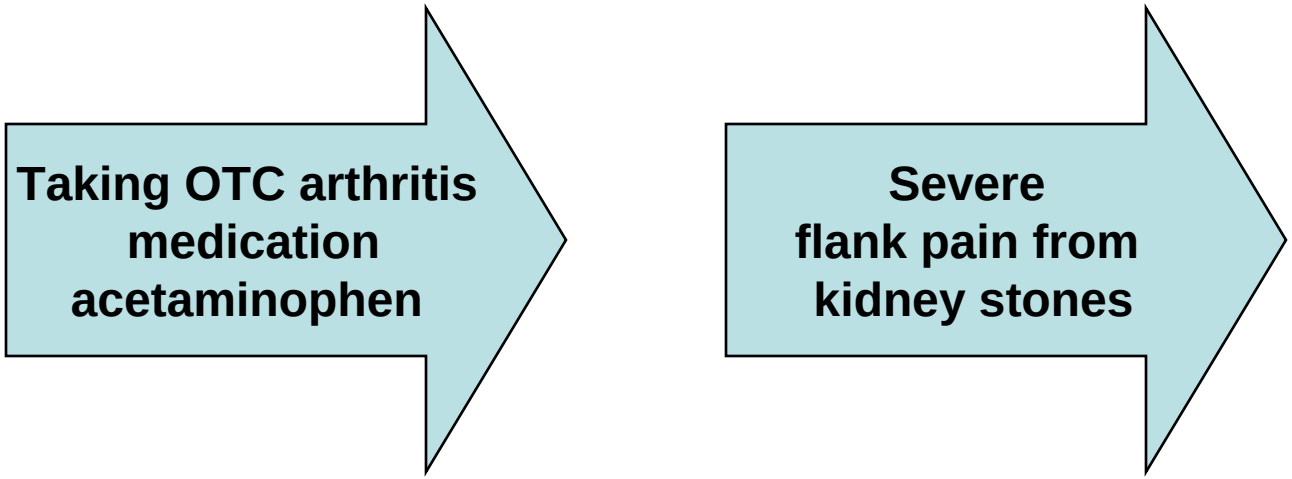
- **www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely**
- **www.fda.gov/cder/drug/analgesics**
- **www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm092139.htm**

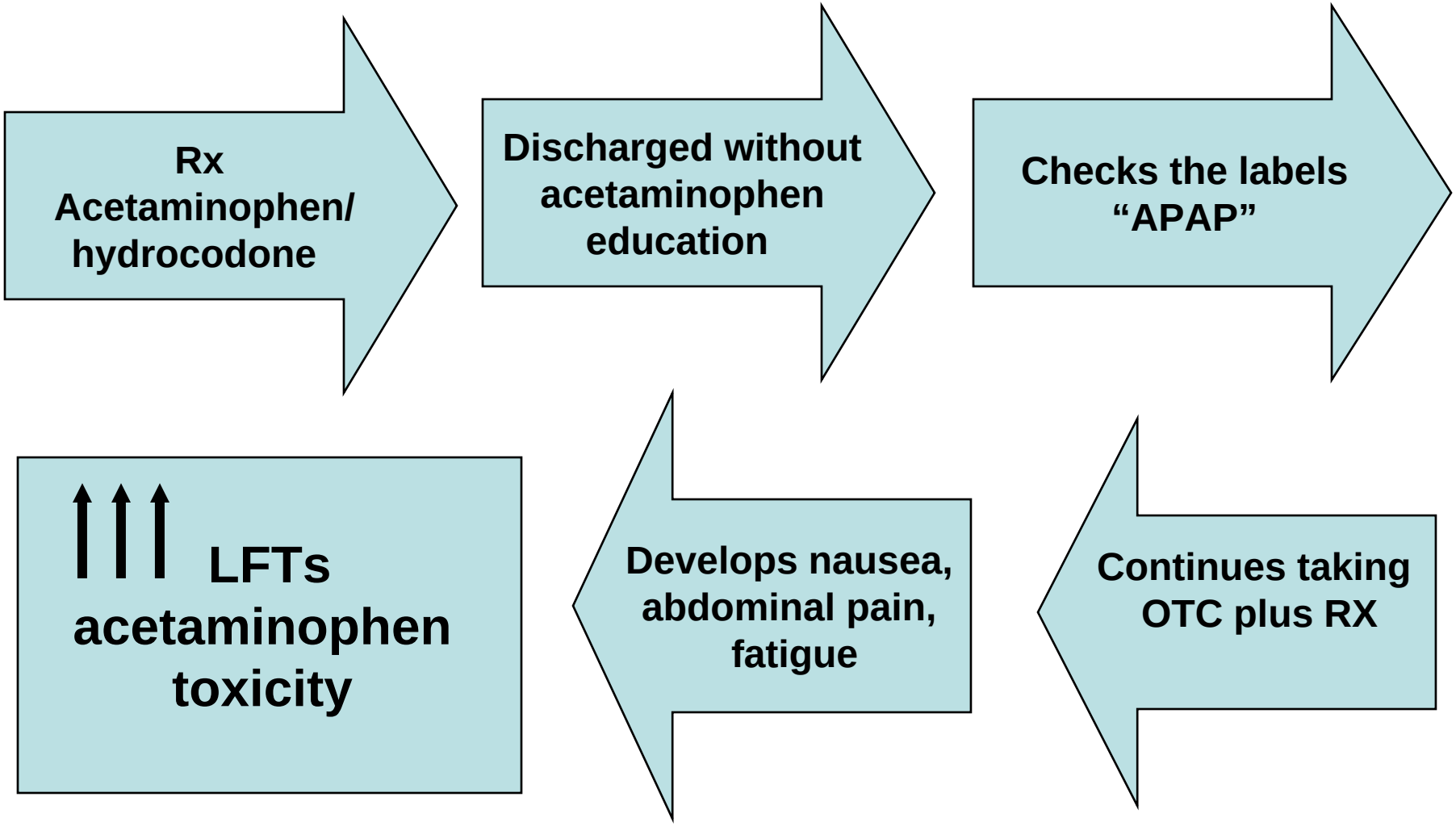
Comprehension and Behavioral Factors Associated with OTC Medication Misuse

Laura Shay, PhD, RN
Captain, USPHS
Social Science Analyst
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products

Fictitious Example Case

- Mrs. Jones is 62 years old
- Good health




Rx
Acetaminophen/
hydrocodone
Discharged without
acetaminophen
education
Checks the labels
“APAP”
Continues taking
OTC plus RX
Develops nausea,
abdominal pain,
fatigue
↑↑↑ LFTs
acetaminophen
toxicity

Outline

- Consumer knowledge about products containing acetaminophen and liver warnings
- Possible factors associated with OTC medication misuse

Consumer Knowledge about Products Containing Acetaminophen and Liver Warnings

Surveys on Consumer Knowledge about Products Containing Acetaminophen and Liver Warnings

- Stumpf et al. 2007 (n=104) adults-clinic
  - Survey conducted: December 2003
  - Objective : If the voluntary label revisions for acetaminophen containing products following the 2002 advisory committee meeting had any impact on consumer knowledge about acetaminophen.
  - Voluntary label changes:
    - highlight active ingredients
    - new liver warnings-dangers of higher doses
  - Unknown how many participants had seen label changes-market place in transition

Surveys on Consumer Knowledge about Products Containing Acetaminophen and Liver Warnings

- Chen, Schneider & Wax. 2002 (n=102) adults-ER
  - Survey conducted: March 2000
  - Study Objective : To evaluate knowledge about acetaminophen
  - Conducted prior to voluntary changes to the label
  - Only liver warning at that time:
    - Alcohol warning

      "If you consume 3 or more alcoholic drinks every day ask your doctor whether you should take acetaminophen or other pain relievers or fever reducers. Acetaminophen may cause liver damage."

Consumer Knowledge about Products Containing Acetaminophen and Liver Warnings

- Study design both surveys
  - Choose from a list of products which products contain acetaminophen
  - Choose from a list of problems which ones are associated with taking too much acetaminophen
- Study limitations
  - Both surveys: "I don't know" option not included
  - Stumpf survey: 2 questions that stated Tylenol is acetaminophen before participants selected from a list of products that contain acetaminophen

Results

	% who thought product contained acetaminophen		
Survey	**Rx Acetaminophen/ opioid**	**OTC without acetaminophen**	**OTC with acetaminophen**
Chen, Schneider & Wax 2002 n=103	**Percocet 13% Percodan 6% Vicodin 6% Darvon 4%**	**Motrin 36% Advil 27% Bayer (aspirin) 11%**	**Excedrin 27%**
Stumpf et al. 2007 n=104	**Vicodin 14% Darvocet 10% Tylox 9% Lorcet 4% Darvon 4%**	**Motrin 19% ibuprofen 12% Aleve 11% Sudafed 11% Benadryl 7%**	**Tylenol 71% Tylenol PM 50%**

Results

Survey	% Understanding APAP	% aware alcohol related to acetaminophen toxicity	% aware liver problems
Chen, Schneider & Wax 2002 n=103	15%	73%	49%
Stumpf et al. 2007 n=104	Not asked	Not asked	43%

Study Looking at ER Discharge Instructions

- Osborne & Bryant (2003) study
  - Methods:
    - Retrospective chart review (n=108)
    - 18 days of emergency room visits
    - Pts discharged on acetaminophen/opioid combinations
  - Results:
    - No patients were discharged with written instructions to reduce or discontinue use of other acetaminophen containing medications

Possible Factors Contributing to OTC Medication Misuse

Awareness about Active Ingredients

- Some consumers are not aware of active ingredients
  - National Council on Patient Information and Education (NCPIE) 2002 survey (n=1,011)
    - 66% reported not buying an OTC medication based on active ingredient
    - 66% who took an OTC medication for their headache could not correctly identify the active ingredient

Reading the OTC Label

- Some consumers don't read the OTC label
  - not reading all or part of the OTC label
    - 5% NCPIE 2002 survey (n=1,011)
    - 32% Alexander, Mohajir & Meltzer 2005 survey (n=553)
    - 10% Eiland, Salazar & English 2008 survey (n=246)
  - 45% Chen, Schneider & Wax 2002 survey (n=103) reported never reading acetaminophen/Tylenol labels regarding:
    - maximum daily dose
    - side effects

Perceptions about Side Effects

- Some consumers have the perception that OTC medications do not have side effects
  - 41% believe OTC medicines are “too weak to cause any problems”
    - NCPIE 2002 survey (n=1,011)
  - 42% did not believe that OTC pain relievers could have side effects when combined with other medications
    - Cham et al. 2002 survey (n=213)
  - 16% believed most OTC drugs do not have side effects
    - Alexander, et al. 2005 survey (n=553)
    - 24% surveyed receiving training to become home health aids

OTC Medication Dose

- Some consumers report taking more OTC medication than directed
  - 33% NCPIE 2002 survey (n=1,011)
  - 57% Kalsher & Woglater 2002 survey (n=330)
  - 22% Alexander, Mohajir & Meltzer 2005 survey (n=553)

OTC Medication Dose

- Of the 33% who reported taking more OTC medication than directed in the NCPIE 2002 survey:
  - 68% had severe symptoms
  - 64% did not get any better taking the recommended dose
  - 38% had taken the prescription version of the medicine before
  - 29% believed it would bring more relief more quickly

Dosing Children

- Reasons dosing errors occur:
  - Difficulty understanding the directions on the label
    - Lokker et al. 2009
    - Yin et al. 2008
    - Frush et al. 2004
    - Li, Lacher & Crain 2000
    - McMahon, Rimsza & Curtis 1997
    - Simon & Weinkle 1997
    - Rivera-Penera et al. 1997
  - Measuring device errors
    - Yin et al. 2009
    - Frush et al. 2004
    - McMahon, Rimsza & Curtis 1997
    - Simon & Weinkle 1997
    - Rivera-Penera et al. 1997
    - Litovitz 1992

Dosing Children

- Measuring device errors
  - Dosing cup
    - Teaspoon/tablespoon confusion on cups markings
    - Assumption that a full cup is a dose
  - Oral dosing syringe
    - Greater accuracy
    - When there is an error, under dosing is most common

Oral Dosing Syringe Versus Dosing Cup

Study	Sample	Syringe %correct	Cup %correct
Mandlon-Kay 2000	**n=130 caregivers**	**92%**	**85%**
		%excessive dose not described	**%excessive dose not described**
Sobahni et al. 2008	**n=96 caregivers**	**67%**	**15%**
		0% excessive dose	**85% excessive dose**

Studies Looking at New Dosing Directions

Study	Sample	Control	Experimental group
Yin et al. 2008	n=245 Rx liquid med PRN	Standard instruction (n=46)	Pictogram instructions+ teach back (n=37)
		24 gave higher dose 12 gave lower dose	10 gave higher dose 2 gave lower dose
Frush et al. 2004	n=101 OTC liquid med PRN	Standard OTC directions (n=50)	Color coded dosing (n=51)
		19 gave higher dose 17 gave lower dose	0 gave higher dose 1 gave lower dose

Dosing Children

- Different concentrations
  - Infant drops 100mg/ml (80mg/0.8ml)
  - Children suspension 32mg/ml (160mg/5ml)
- Confusion about the different concentrations
  - 51%-65% reported that the children's liquid was more concentrated than the infant drops
    - NCPIE 2002 survey: n=1,011
    - Barrett & Norton 2000 survey: n=138

"Children are larger than infants and therefore the medicine ought to be more concentrated."

Barrett & Norton 2000

Drug Advertising

- FDA regulates Rx advertising
- Federal Trade Commission (FTC) regulates OTC advertising
  - requires drug claims to be accurate and non-misleading
  - does not require listing of possible side effects or active ingredients

Drug Advertising

- The average American views > 30 hours of OTC and Rx pharmaceutical advertisements annually (Brownfield et al. 2004)
  - 18, 906 advertisements appeared in 504 hour sample of network television in 2001 (Brownfield et al. 2004)
    - 907 OTC drugs
    - 428 Rx drugs

- Consumer research on the effects of OTC drug advertising on consumer knowledge or perceptions is lacking

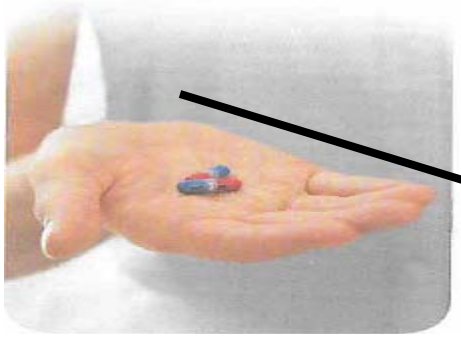
Your liver performs 500 critical functions.

And taking too much of some medications, including BRANDx can cause it harm. So always follow the recommended dose, and don't take more than one medication that contains acetaminophen, the medicine in BRANDx Your liver will appreciate the respect.

www. BRANDx.com/liver

Feel better,

BRANDx



HealthyShape

GIRLS GOTTA

BURN

Just add in

Interval traini
ways to burn
also a great wa

FOR NEW

Pick up the pace
1. Walk at a bris
2. Run for 3 min
challenging pac
3. Power-walk f
4. Repeat steps
5. Walk at an ea
FYI: As you gain
running and less

FOR SEAS

Go faster, strong
1. Walk at a brisk
at an easy pace
2. Run as hard a
3. Run at an easy
4. Repeat steps
5. Cool down wi
and 3 minutes o
FYI: If you focus
your efficiency w
will, too.

TEAM OF T

Girl powe

"I have little wil
power to keep
training on my
own. If not for t
rest of the Cha-
Cha Running Cl
I'd be really out
of shape!" says
Wendy Bentzon
39, of Saylorsbu
excuse to get o
an incredible gr
wearing outrag

RITE US,
Girls
members will receiv

181

Health magazine: May 2009

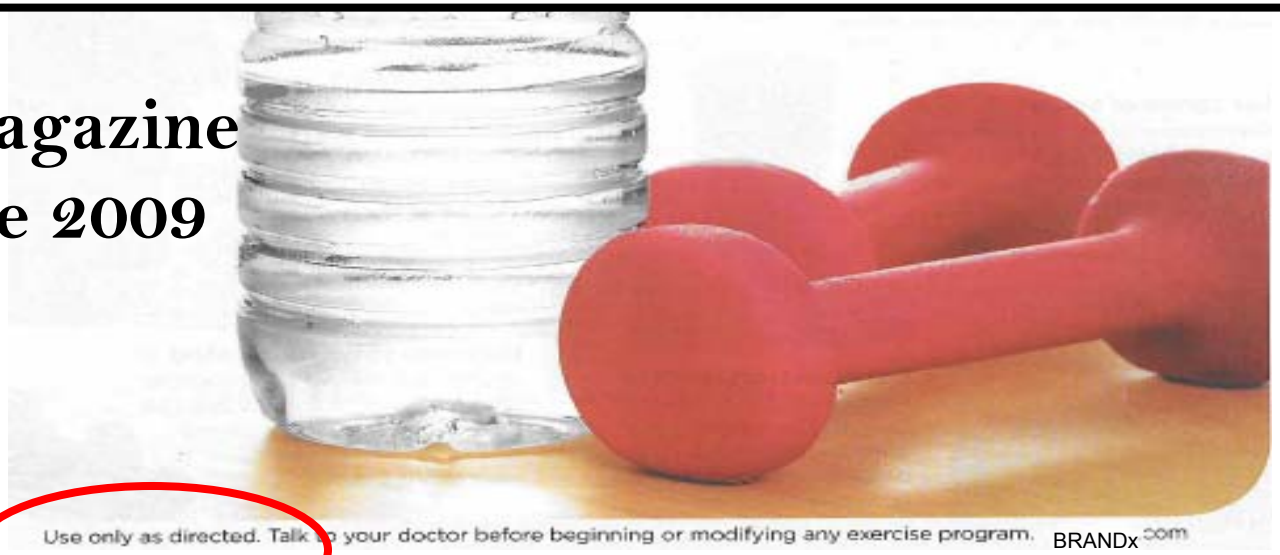
Arthritis pain might sound like a reason to skip your daily walk.
But actually, it's the reason you shouldn't. Light aerobic exercise helps your joints from getting stiff and weak. BRANDx Arthritis pain helps to. It works with your body to quiet the pain as effectively as prescription ibuprofen. In fact, more doctors recommend BRANDx than any other brand of pain reliever. So while arthritis is certainly no walk in the park, at least relief can be.

Feel better,

BRANDx

Arthritis Pain

AARP magazine
May-June 2009



Health magazine: May 2009

Summary

- Many surveyed did not know which products contain acetaminophen or that “APAP” =acetaminophen

- Some surveyed believed that OTC medications do not have side effects and >50% surveyed did not know that too much acetaminophen can cause liver damage

- There were multiple reasons reported for taking more OTC medication than directed

Summary

- Dosing errors in children
  - Difficulty understanding the directions on the label
  - Measuring device errors
  - Confusion about product concentrations
  - Oral dosing syringes and innovative dosing directions appear to improve accuracy
- Opportunities for improvement
  - Health care professionals communication with patients
  - OTC advertising

References

Stumpf JL, Skyles AJ, Alaniz C, Erickson SR. Knowledge of appropriate acetaminophen doses and potential toxicities in an adult clinic population. *J Am Pharm Assoc (2003).* Jan-Feb 2007;47(1):35-41.

Osborne ZP, Bryant SM. Patients discharged with a prescription for acetaminophen-containing narcotic analgesics do not receive appropriate written instructions. *Am J Emerg Med.* Jan 2003;21(1):48-50

National Council on Patient Information and Education (NCPIE): Attitudes and Beliefs about the Use of Over-the-Counter Medicines; A Dose of Reality: National Survey of Consumer Health Professionals 2002.

Barrett TW, Norton VC. Parental knowledge of different acetaminophen concentrations for infants and children. *Acad Emerg Med.* Jun 2000;7(6):718-721.

References

Eiland LS, Salazar ML, English TM. Caregivers' perspectives when evaluating nonprescription medication utilization in children. *Clin Pediatr (Phila).* Jul 2008;47(6):578-587

Chen L, Schneider S, Wax P. Knowledge about acetaminophen toxicity among emergency department visitors. *Vet Hum Toxicol.* Dec 2002;44(6):370-373.

Litovitz T. Implication of dispensing cups in dosing errors and pediatric poisonings: a report from the American Association of Poison Control Centers. *Ann Pharmacother.* Jul-Aug 1992;26(7-8):917-918.

Yin HS, et al. Randomized Control Trial of Pictogram-Based Intervention to Reduce Liquid Medication Dosing Errors and Improve Adherence Among Caregivers of Young Children. *Arch Pediatr Adolesc Med.* Sept. 2008;162(9):814-822.

References

Rivera-Penera T, Gugig R, Davis J, et al. Outcome of acetaminophen overdose in pediatric patients and factors contributing to hepatotoxicity. *J Pediatr.* Feb 1997;130(2):300-304.

Li SF, Lacher B, Crain EF. Acetaminophen and ibuprofen dosing by parents. Pediatric Emergancy Care. December 2000; 16(6): 394-397

Brownfield ED, Bernhardt JM, Phan JL, Williams MV, Parker RM. Direct-to-consumer drug advertisements on network television: an exploration of quantity, frequency, and placement. *J Health Commun.* Nov-Dec 2004;9(6):491-497

Simon HK, Weinkle DA. Over-the-counter medications. Do parents give what they intend to give? *Arch Pediatr Adolesc Med.* Jul 1997;151(7):654-656.

References

Lokker, N. et al. Parental Misinterpretations of Over-the-Counter Pediatric Cough and Cold Medication Labels, *Pediatrics*. June 2009;123(6):1464-1471.

Sobhani, P. et al. Accuracy of Oral Liquid Measuring Devices: Comparion of Dosing Cup and Oral Dosing Syringe. *The Annals of Pharmacotherapy*, January 2008, Vol. 42: 46-52.

Cham E, Hall L, Ernst AA, Weiss SJ. Awareness and use of over-the-counter pain medications: a survey of emergency department patients. *South Med J.* May 2002;95(5):529-535.

Alexander GC, Mohajir N, Meltzer DO. Consumers' Perceptions About Risk and Access to Nonprescription Medications. *Journal of the American Pharmacists Association.* 2005;45(3):363-370.