

*Significance of the Black Box  
Warning: Is It Different in Seniors*



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# CAFERGOT

(ergotamine tartrate and caffeine)

SUPPOSITORIES, USP

Rx Only

## WARNING

Serious and/or life threatening peripheral ischemia has been associated with the coadministration of CAFERGOT with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of CAFERGOT, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated (*See also CONTRAINDICATIONS and WARNINGS section*)

# *Boxed Warnings*

## *21 CFR 201.57 (e)*

***Labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug: a causal relationship need not have been proved....***

# *Boxed Warnings*

## *21 CFR 201.57 (e)*

*Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displaced box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.*

# *Black Box Facts*



- Intended to provide alert regarding high risks associated with drug.
- Can only be issued following an FDA mandate.
- Black Box warnings emphasize significant and serious safety data regarding prescription drugs.
- Warnings may include: potential adverse events, drug interactions, dosing information, monitoring and administration requirements, and at-risk populations

# *Black Box Facts*

- New Black Box data available at marketing or may be added post-marketing (reflecting the dynamic nature of a safety profile post-marketing)
- Safety profile of a NCE is limited by premarketing data
  - number of patients (~3,000)
  - homogeneous population
  - concurrent pharmacotherapy
  - latent side effects

# *Black Box Facts*



- Must be cited in all advertising and included in package inserts
- Distribution of medication guides
- Impact on prescribing

# *The Imperfect Nature of BBWs*



- Criteria for development
- Supportive evidence
- Efficacy as risk communication tool
- Inconsistent presentation
- Adherence
- Resources for keeping current
- Prescriber notification
- Patient notification/materials
- Market Withdrawals

# *Black Box Warnings in Labeling Results of a Survey: 206 Drugs*

*Beach JE et al. Food and Drug Law Journal 1998; 53: 403-411*

Type of Warning	No.	375 Warnings	206 Drugs
Early detection of a reversible condition	47	12%	23%
Avoidance of high risk patients	95	25%	46%
Risk outweigh benefits	36	10%	18%
Dosing/Drug Interaction	74	20%	36%
Special training/Physical Setting	66	18%	32%
Drug Administration	57	15%	28%

*Mean of 1.83 BBW per drug*

# *Black Box Warnings in Labeling Results of a Survey: 206 Drugs*

*Beach JE et al. Food and Drug Law Journal 1998; 53: 403-411*

<b>Type of Warning</b>	<b>No.</b>	<b>Percentage</b>
<b>Postmarketing Reports</b>	<b>133</b>	<b>52.4%</b>
<b>Clinical Trials</b>	<b>73</b>	<b>28.7%</b>
<b>Epidemiology Reports</b>	<b>24</b>	<b>9.4%</b>
<b>Other</b>	<b>24</b>	<b>9.4%</b>
<b>Total</b>	<b>254</b>	<b>100%</b>

# *Black Box Drugs & U.S. Market Withdrawals*

[JAMA 2002; 287(17):2215-2220]

- Examined frequency/timing of Black Box warnings (BBW) or drug withdrawals from U.S. market: 1975 to 2000
- Source: PDR
- 548 NCE's approved in U.S. [1975 -1999]
- 56 (10.2%) acquired new black box warning or withdrawn from market
- 45 (8.2%) acquired  $\geq 1$  new BBW post marketing
- 16 (2.9%) drugs withdrawn from market (5 with new BBW)

# *Black Box Drugs & U.S. Market Withdrawals*

[JAMA 2002; 287(17):2215-2220]

- Half of market withdrawals occurred within 2 yrs of approval
- Half of package inserts changed with 7 yrs
- Most common changes
  - cardiovascular: 21%
  - hepatic: 19%
  - hematologic: 16%
  - pregnancy risk: 11%

# *US Drug Withdrawals*

*1980-2007*

- Ticranyfen (1980)
- Benoxaprofen (1982)
- Zomepirac (1983)
- Nomifensine (1986)
- Suprofen (1987)
- Encainide (1991)
- Temafloxacin (1992)
- Flosequinan (1993)
- Dexfenfluramine (1997)
- Fenfluramine (1997)
- Terfenadine (1998)
- Mibefradil (1998)
- Bromfenac (1998)
- Grepafloxacin (1999)
- Astemizole (1999)
- Alosetron\* (2000)
- Phenylpropanolamine (2000)
- Troglitazone (2000)
- Cisapride\*\* (2000)
- Rapcuronium (2001)
- Cerivastatin (2001)
- Rofecoxib (2004)
- Natalizumab\* (2005)
- Fanolesomab 99mTc (2005)
- Pemoline (2005)
- Valdecoxib (2005)
- Pergolide (2007)
- Tegaserod (2007)

# Drug Withdrawals

## 1999-2002

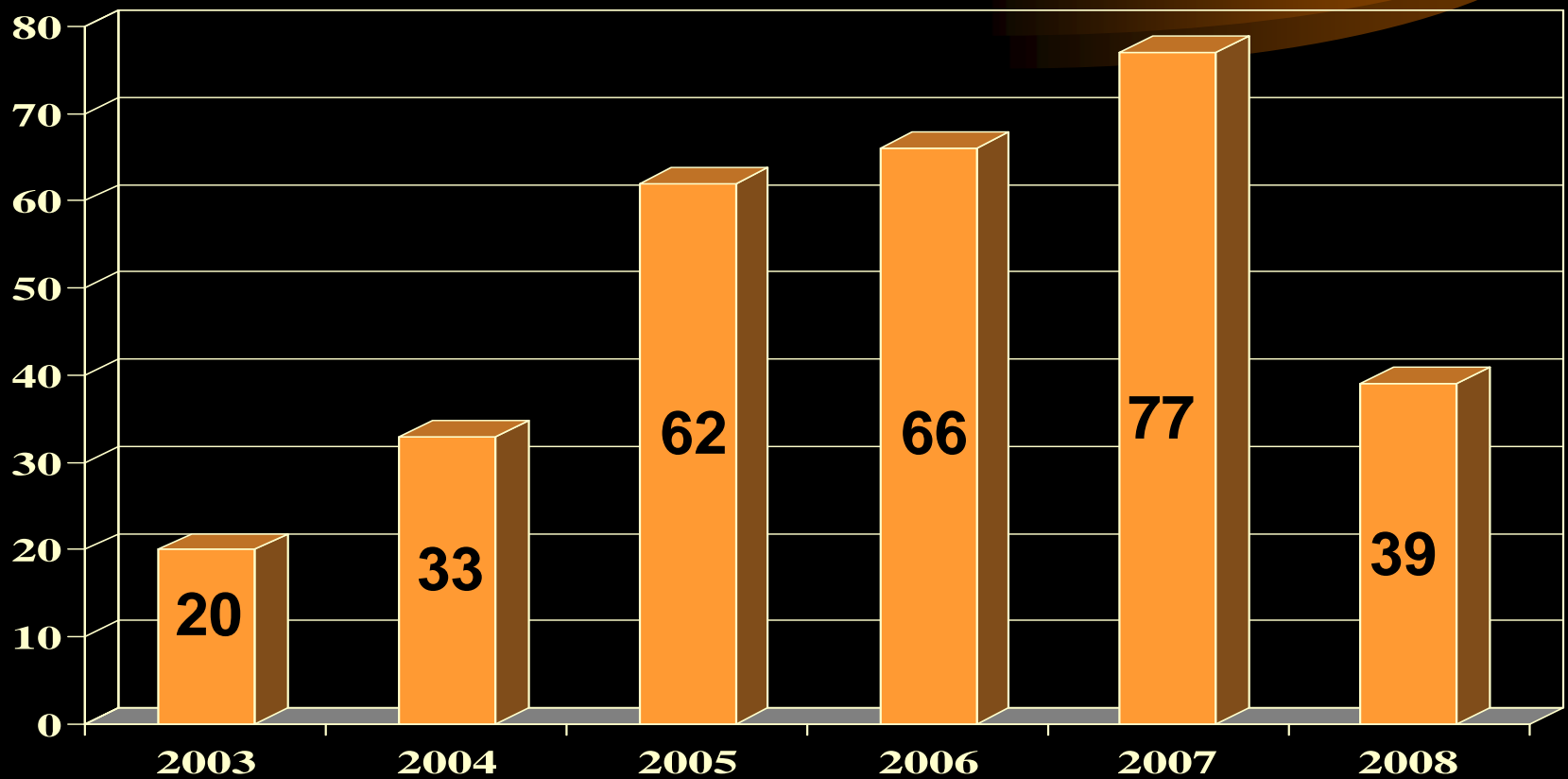
Drug Name	Drug Class/Use	Removal Year	Market Life (Months)	Safety Issue
Grepafloxacin	Antibiotic	1999	14	QT prolongation
Astemizole	Anthistamine	1999	120	QT prolongation interactions
Alosetron*	Irritable bowel	2000	9	Ischemic colitis
PPA	OTC (diet, cough)	2000	Yrs	Hemorrhagic stroke
Troglitazone	Antidiabetic	2000	12	Hepatic
Cisapride**	GI motility	2000	60	QT prolongation Interactions
Rapacuronium	Anesthesia adjunct	2001	19	Bronchospasm, fatalities
Cerivastatin	Hypolipidemic	2001	30	Rhabdomyolysis

# *Drug Withdrawals*

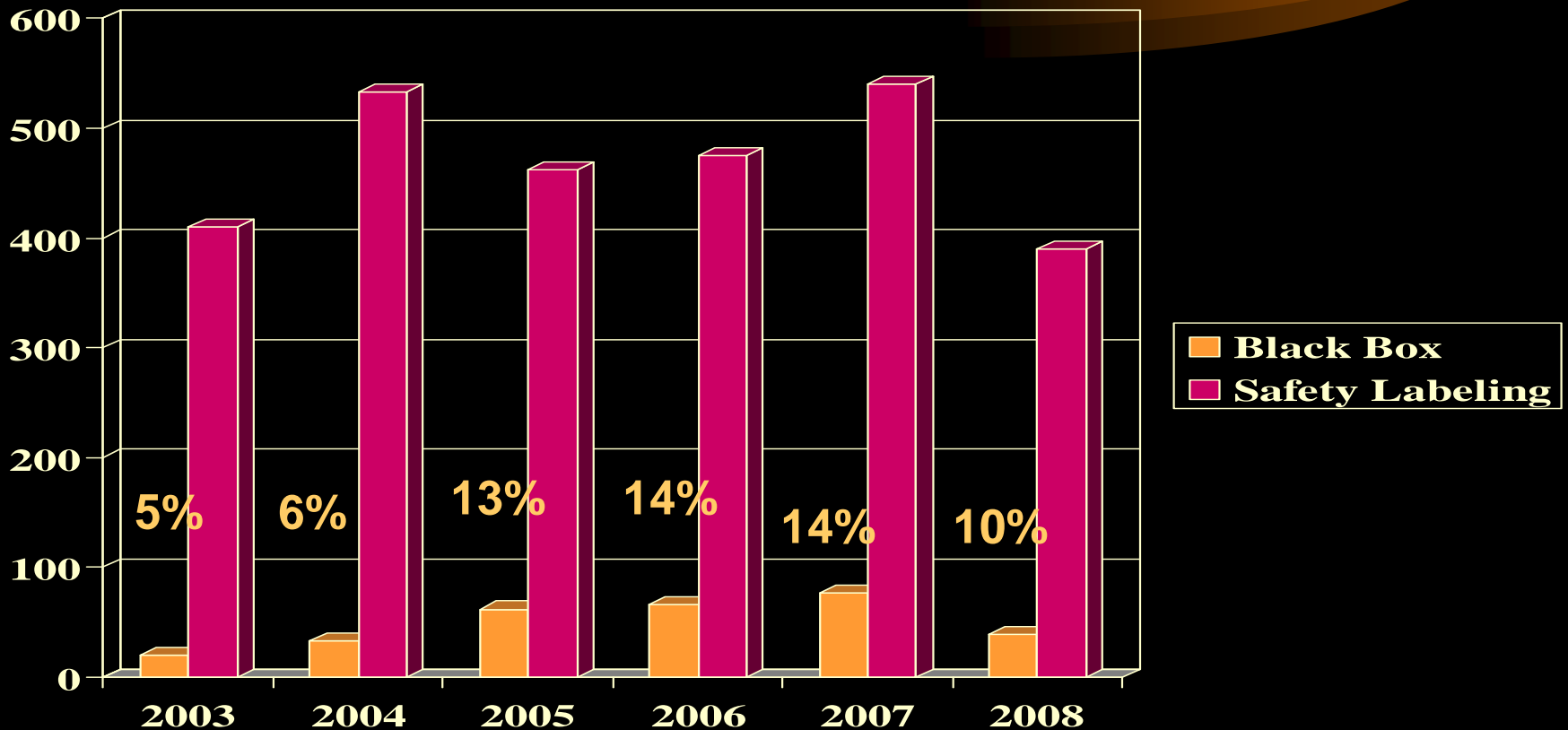
## *2003-2006*

<b>Drug Name</b>	<b>Approval Year</b>	<b>Removal Year</b>	<b>Market Life (Months)</b>	<b>Safety Issue</b>
Rofecoxib	1999	2004	60	Cardiac
Natalizumab*	2004	2005	5	PML
99Tmc Fanolesomab	2004	2005	18	Cardio- pulmonary
Pemoline	1975	2005	yrs	Hepatic
Valdecoxib	2001	2005	42	Cardiac

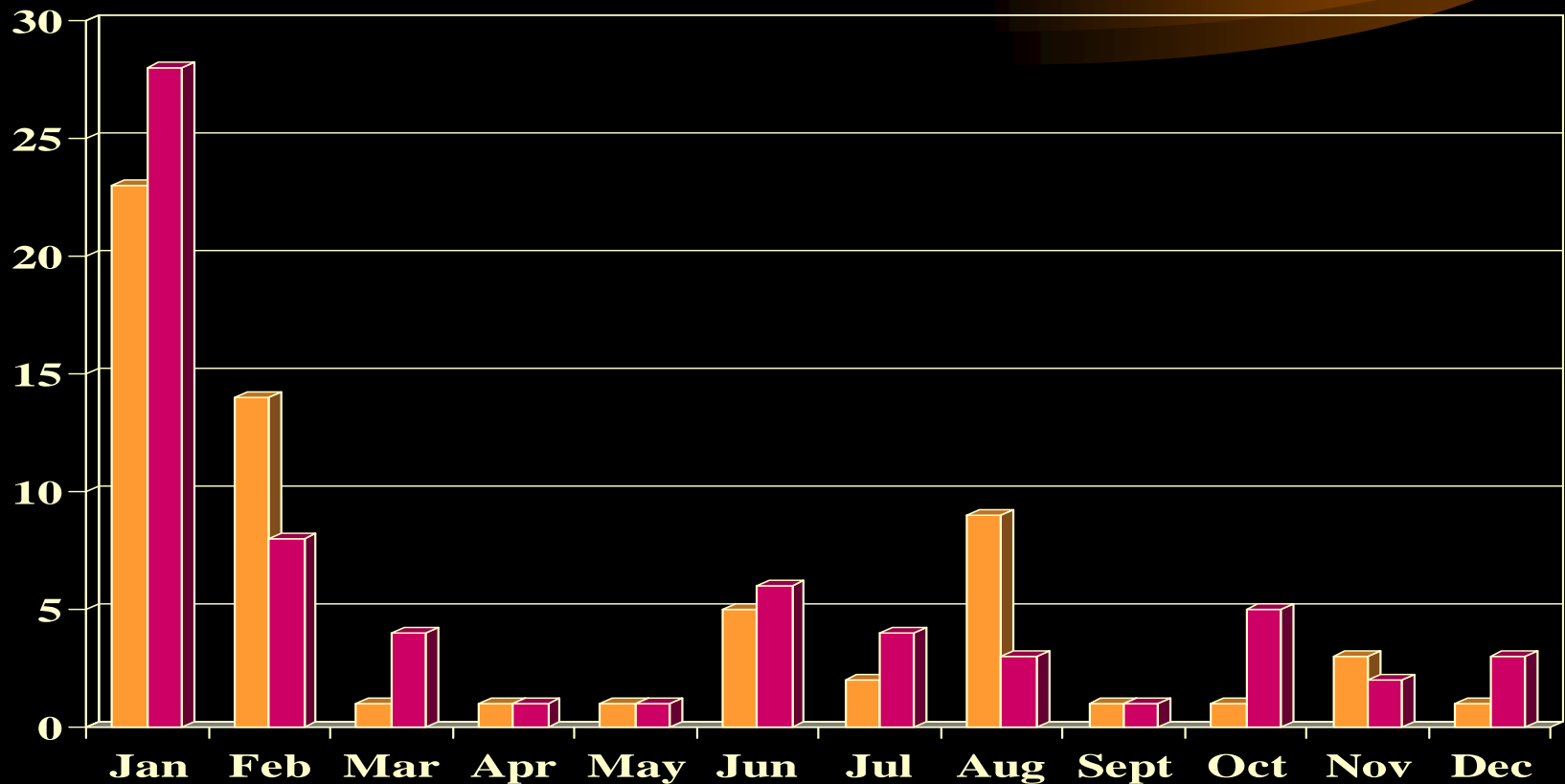
# *Safety Labeling Changes Approved by FDA: Black Box Warnings*



# *Safety Labeling Changes Approved by FDA: Total vs Black Box Warnings*



# *Safety Labeling Changes Approved by FDA: Black Box Warnings 2005-2006*



# *Black Box Warnings Class Labeling 2005-2008*



- Fluoroquinolones
- NSAIDs: cardiovascular
- Antipsychotics : mortality risk in dementia
- Antidepressants : suicidal ideation
- Estrogens : WHI updates

# *Black Box Warnings*

2006

- Bevacizumab
- Cetuximab
- Dextroamphetamine sulfate
- Docetaxel
- Fluticasone/Salmeterol
- Formoterol
- Hydromorphone
- Infliximab
- Lenalidomide
- Metformin
- Methadone
- Natalizumab\*
- Nimodipine
- Pimecrolimus
- Tacrolimus
- Thalidomide
- Tipranivir
- Tolcapone
- Trastuzumab
- Valproic Acid/Derivatives
- Warfarin\*

# *Black Box Warnings*

2007

- ACE Inhibitors
- Acitretin
- Adalimumab
- Alemtuzumab
- Antidepressants (SSRIs, TCAs)
- Antipsychotics (conventional)
- Bosentan
- Cetuximab
- Entecavir
- ESAs\*
- Fentanyl
- Gadolinium Contrast Agents\*
- Idursulfurase
- Ketorolac
- Methamphetamine
- Mycophenolate
- Omalizumab\*
- Perflutren\*
- Pioglitazone
- Protamine\*
- RAlloxifene\*
- Rituximab
- Rosiglitazone
- Telithromycin\*
- Tenofovir
- Tinidazole
- Tolcapone

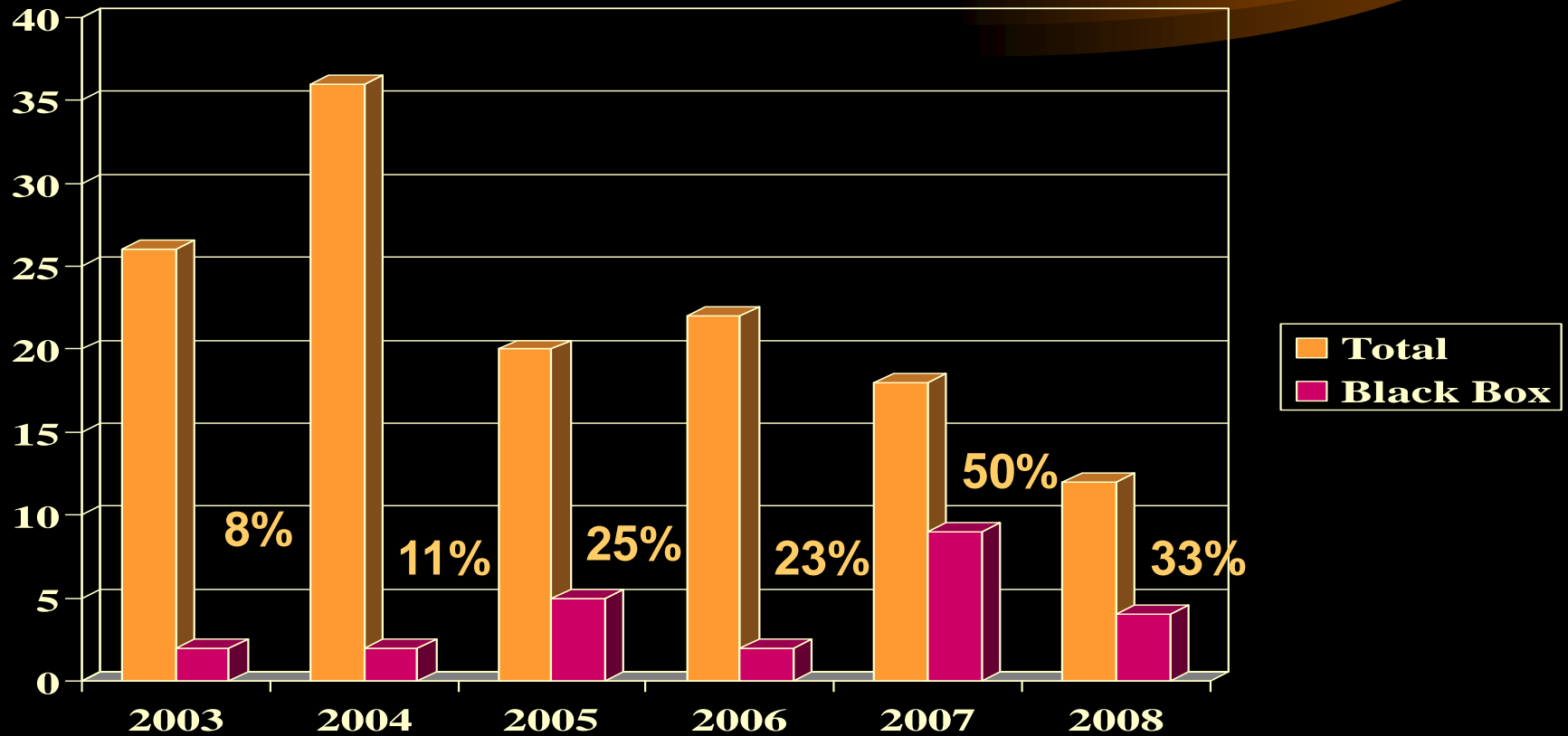
# *Black Box Warnings*

2008

- Abacavir
- ACE Inhibitors
- Antipsychotics (conventionall)\*
- Atomoxetine
- Becalpermin\*
- Clindamycin
- Darbepoetin
- Efalizumab\*
- Emtracitabine
- Entecavir
- Epoetin
- Fentanyl
- Fluoroquinolones\*
- Lapatinib\*
- Laronidase
- Nevirapine
- Perflutren
- Rituximab
- Tenofovir
- Trastuzumab

# *Drug Approvals*

## *Total vs Black Box Warnings*



# *Approval Times: Priority & Standard NMEs and Biological Agents*

<b>Year</b>	<b>Number Priority Drugs (BBx)</b>	<b>MAT/ MRT (mos)</b>	<b>Number Standard Drugs (BBx)</b>	<b>MRT (mos)</b>	<b>MAT (mos)</b>
<b>2004</b>	<b>21 (3)</b>	<b>6.0</b>	<b>15 (1)</b>	<b>16.0</b>	<b>24.7</b>
<b>2005</b>	<b>15 (4)</b>	<b>6.0</b>	<b>5 (1)</b>	<b>15.8</b>	<b>23.0</b>
<b>2006</b>	<b>10 (3)</b>	<b>6.0</b>	<b>12 (2)</b>	<b>12.5</b>	<b>13.7</b>

*BBx = Black Box Drug Approved*

*MAT = median total approval time*

*MRT = median FDA review time*

# *New Drugs with Black Box Warnings: 2005-2008*

- Alglucosidase alfa
- Aliskiren
- Alvimopan
- Arformeterol
- Ambrisentan
- Desvenlafaxine
- Eculizumab
- Entecavir
- Gadoxetate
- Idursulfase
- Ixabepilone
- Lenalidomide
- Lisdexamfetamine
- Nelarabine
- Nebivolol
- Nilotinib
- Paliperidone
- Panitumumab
- Pramlintide
- Tipranavir
- Telbivudine
- Tetrabenazine

# *Implications for Prescribing & Patient Safety*

- Postmarketing surveillance is essential to optimize safety during early market life of drug (e.g., ADRs, off-label use) due to limited premarketing data
- Liability related to prescribing outside of PI for safety reasons
- Notification of new BBW data and changes (FDA website, e-lists, Dear health professional letters)

# *Black Boxes Related to Elderly*

- Increased mortality in elderly patients with dementia related psychosis (conventional/atypical antipsychotics)
- Increased risk of pulmonary fibrosis (bleomycin)
- Nephro/Neurotoxicity (gentamicin, kanamycin)
- Emergence reactions (ketamine)
- Gastrointestinal risk (NSAIDs)

# *Implications for Prescribing & Patient Safety*

- Dissemination of BBW information ( email safety alerts)
- Ensuring adherence to BBWs (development of patient care plans, policies, criteria for use)
- Imbedded drug information at point of care (Online formularies, computerization of data upon refills)
- Patient counseling

# *Mortality Risk and Dementia*

- Elderly patients with dementia related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo.
- Analyses of seventeen placebo controlled trials (modal duration of 10 weeks, largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug treated patients of between 1.6 to 1.7 times that seen in placebo treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug treated patients was about 4.5% compared to a rate of about 2.6% in the placebo group.
- Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

# *Mortality Risk and Dementia*

- Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality.
- The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.
- This drug is not approved for the treatment of patients with dementia-related psychosis (See WARNINGS in package insert).

# *Mortality Risk and Dementia*

[http://www.fda.gov/cder/drug/InfoSheets/HCP/antipsychotics\\_conventional.htm](http://www.fda.gov/cder/drug/InfoSheets/HCP/antipsychotics_conventional.htm)

- Canadian retrospective cohort study
- 27,259 adults,  $\geq 66$  years of age, with a diagnosis of dementia
- Atypical antipsychotic vs no antipsychotic  
ATAP vs conventional antipsychotic
- AT-AP were associated with increased mortality as compared to no antipsychotic (30 days to 180 days. )
- conventional antipsychotic > atypical antipsychotic use.

# *BBWs: What's Next?*

- New labeling modifications
  - Highlights of Prescribing Information
  - Prescriber friendly (bullet summaries)
  - Examples : [Zolinza](#) [Januvia](#)
- Class labeling
- Participation of HCPs in labeling language.

# *BBW Information Resources*

- FDA Medication Safety Sites
  - <http://www.fda.gov/medwatch/safety.htm>
- FDA E-mail notification
  - <http://www.fda.gov/medwatch/elist.htm>
- Black Box List
  - <http://www.formularyproductions.com/blackbox>

# *Black Box Warnings*



*Questions*