

# Review of OTC Cough and Cold Medicines

## Safety Data

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# Coughs and Sneezes ...



# Health Canada Decision on OTC Cough & Cold Medicines

- When assessing risk Committee asked to consider -

*"The severity of the adverse effects and the likelihood of harm. "*

# Antihistamines - 1

- **Alkylamines:** *brompheniramine, chlorpheniramine, triprolidine* - highly potent H1 antagonists, significant sedative actions, paradoxical stimulation esp in children.
- **Monoethanolamines:** *clemastane, diphenhydramine, doxylamine* - pronounced sedative and muscarinic actions, low incidence GI ADRs.
- **Ethylenediamines:** *antazoline, mepyramine* - selective H1-antagonists, moderate sedation, gastric disturbances, skin sensitisation.

# Antihistamines - 2

- **Phenothiazines:** *promethazine* - significant sedative, and antimuscarinic effects, photosensitivity reactions.
- **Piperazines:** *cetirizine, cyclizine* - moderate sedative actions.
- **Piperidines:** *azatidine, loratadine* - highly selective for H1 receptors, moderate or low sedation.

Martindale 2009

# Antihistamines - 3

- Sedating :
  - CNS depression, drowsiness to deep sleep, incoordination.
  - Paradoxical stimulation
  - Headache, psychomotor impairment, antimuscarinic effects.
  - GI - nausea, vomiting, diarrhoea, or epigastric pain.

# Antihistamines - 4

- Sedating cont'd - rare ADRs
  - palpitations and arrhythmias
  - rashes, hypersensitivity reactions, photosensitivity
  - blood disorders, including agranulocytosis, haemolytic anaemia
  - convulsions

# Sympathomimetics

(decongestants - pseudoephedrine, phenylephrine, xylo- and oxymetazoline)

CVS - Hypertension, palpitations, tachycardia, arrhythmias

- CNS stimulation- insomnia, tremor, hallucinations (rare)
- Hypersensitivity



# Antitussives

- **Dextromethorphan & Pholcodine**
  - CNS, - drowsiness, fatigue, dizziness, dystonia, psychosis, hallucinations, serotonin syndrome (dextromethorphan interaction), drug abuse, respiratory depression
  - Anaphylaxis, rashes
  - GI - constipation

# Expectorants

- **Guaifenesin**
  - GI, discomfort, nausea, vomiting
  - Urolithiasis (abuse)
  - CI in porphyria
- **Ipecacuanha**
  - GI, vomiting, haemorrhagic erosions
  - cardiotoxicity
  - abuse

# Mucolytic

- Bromhexine
  - Hypersensitivity - rashes, anaphylaxis
  - GI
  - Hepatic - transient increases in serum transaminases
  - Headache, dizziness, sweating.

# Cough & Cold Medicines

## Overdose effects

- **Antihistamines**

- Children - CNS stimulation, ataxia, excitement, psychoses, hallucinations, convulsions, hyperpyrexia, tachycardia.

- **Pholcodine, dextromethorphan**

- Children - excitation, confusion, extrapyramidal effects, respiratory depression.

- **Sympathomimetics**

Excitement, nervousness, GI effects, nausea, ataxia, hallucinations, convulsions and tachycardia.

# Safety of Cough and Cold Medicines

- Reasons for adverse effects:
  - Adverse reactions and interactions at therapeutic doses
  - Overdose
    - Accidental ingestion by child
    - Medication error, wrong dose etc
      - Parent, iatrogenic
    - Deliberate overdose

# Safety of Cough and Cold Preparations Information Sources - 1

- Placebo-controlled randomised trials
- Non-randomised trials
- Observational studies
- Meta-analyses and major reviews
- Case series, published

# Safety of Cough and Cold Preparations

## Information Sources - 2

- Pharmacovigilance Centres
  - National, international spontaneous adverse reactions reports (Individual Case Safety Reports, ICSRs)
- Poisons Centres
  - Regional, national - requests for advice

## Pharmaceutical Companies

- ICSRs

# Randomised Placebo-controlled trials

None had safety end points

- Likely that only powered to detect difference between placebo and active medicines for very common adverse reactions
- Six trials included 2-6 year olds, one included ibuprofen
- Expected non-serious adverse effects, for most rate not significantly different from placebo.
- Hyperactivity with dextromethorphan noted in two trials, common and dose related in one. (Paul et al, 2004).



# Post-marketing Surveillance Studies

- Pseudoephedrine and hospitalisation:
  - Porta et al. 1983. Puget Sound Group Health Cooperative. Populations surveyed 100.000.
  - 0-19 yr - 81,965 scripts
  - 246 admissions, one seizure (F22) possibly drug related

# Postmarketing Surveillance

- Pseudoephedrine, toxic dose (NB single substance)
- Wezorek et al. Prospective study to determine toxic dose through children who had ingested pseudoephedrine:
- 140 children <6yrs.
  - 30-180 mg
    - drowsiness 21.7%
    - hyperactivity 6.9%
  - >180 mg
    - Drowsiness 15.4% (? Error)
    - Mild hyperactivity 15.4%

# Published Case Reports & Case Series Overdoses

- See Annex 3 in Review of the Safety and Efficacy of Cough & Cold Medicines for Use in Children, by Susan Kenyon
- Deaths,
  - < 2yrs 50
  - > 2yrs 6 (5 accidental, 1 undetermined)
    - » (diphenhydramine 4, benadryl 1, cough mixture + verapamil 1)

# ICSRs and Poisons Centre data

- No reliable denominator data
- Incomplete reporting
  - Number of reports
  - Quality of reports

# American Association of Poison Control Centres

- National Poisoning Data System - 1 Jan 2000 to 30 June 2007
- Analysis of exposure data to gain info and identify root causes
- Number of "contacts, exposures or cases" over 6.5 years for OTC C&C meds in < 12yr olds - **774,960**
- OTC meds most often involved - decongestants (48%), antihistamines (42%), antitussives (32%), expectorant (9%).

# American Association of Poison Control Centres - reasons for exposures - 1

## AAPCC Reasons For Exposures to Cough and Cold Medications

- In Children <12 years (y) of Age (2000-2007)
- Reasons for Medication Exposure

### Inadequate Measures To Keep Medicines Out of the Reach of Children

	0-<2yrs	2-<6yrs	6-<12yrs
	N (%)	N (%)	N (%)
• Product stored inappropriately	1422 (28.43%)	3465 (69.29%)	114 (2.28%)
• Accessed medication in purse or suitcase	628 (27.78%)	1594 (70.50%)	39 (1.72%)
• Product temporarily open	1586 (29.31%)	3677 (67.95%)	148 (2.74%)

# American Association of Poison Control Centres - reasons for exposures - 2

• Therapeutic/Medication Errors	0- <2yrs	2- <6yrs	6- <12yrs
• Other incorrect dose	14447 (31.24%)	22736 (49.16%)	9065 (19.6%)
• Confused units of measure	4922 (32.03%)	7486 (48.72%)	2957 (19.25%)
• More than one product containing same ingredient	2943 (23.52%)	6057 (48.41%)	3513 (28.07%)
• Health professional iatrogenic	610 (64.08%)	249 (26.16%)	93 (9.77%)
• Ten-fold Dosing Error	633 (70.81%)	195 (21.81%)	66 (7.38%)
• Dispensing Cup Error	3867 (30.39%)	6337 (49.8%)	2522 (19.82%)
• Incorrect Form Concentration Given and Dispensed	6325 (34.20%)	8549 (46.22%)	3621 (19.58%)

# American Association of Poison Control Centres - reasons for fatalities

- AAPCC Reasons For Fatal Exposures to Cough and Cold Medications
- In Children <12 years (y) of Age (2000-2007)
- Reasons for Medication Exposure

	0-<2	2-<6	6-<12	0-<12y (N=35)
• Adverse Reaction	2	0	2	4 (12%)
• Intentional Misuse	1	0	0	1 (2%)
• Malicious	5	1	0	6 (17%)
• Therapeutic Error	3	4	0	7 (20%)
• Unintentional General	4	6	0	10 (29%)
• Unknown reason	5	1	1	7 (20%)



# American Association of Poison Control Centres

- Serious (<3%)

- Moderate effect 0.86%
- Major effect 0.04%
- Death 0.0045% (N=35)
- Unable to follow
  - potentially toxic 1.7%

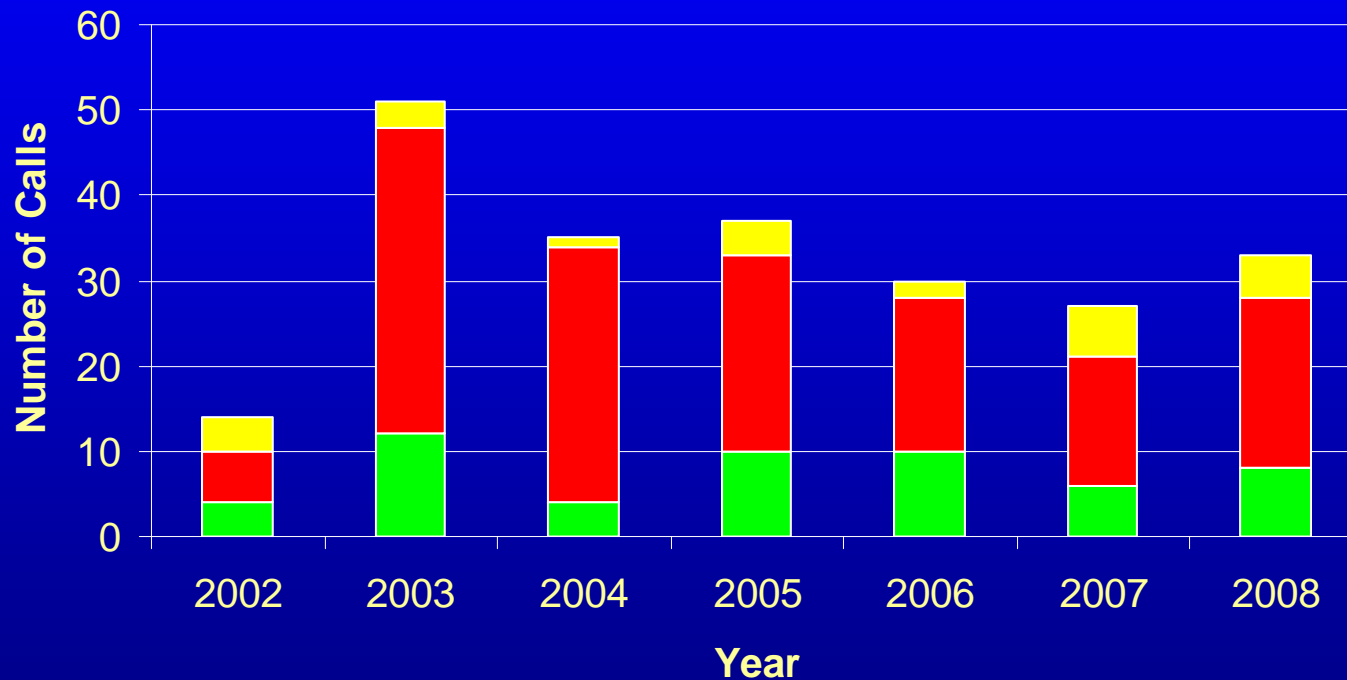
# National Poisons Information Centre UK

- 100,000 calls over 4 yrs for OTC  
C&C preps
- 230 children admitted over 1 year  
period

# NZ Poisons Centre Data

## Cases requiring medical referral

■ <2 years    ■ 2-<6 years    ■ 6 years and above



# NZ Poisons Centre Data

- Greatest proportion of childhood reports (0-16 yrs) was in 2-6 yr group
- Medicines implicated Phenergan (81), Histafen (50), Polaramine and polaramine repetabs (37), Sudomyl (15) and isolated cases of exposure to other medicines
  - \*ie most reports to single ingredient antihistamine preps primarily indicated for allergy.\*

# ADR reports to regulatory authorities/pharmacovigilance centres

- *US, Canada, UK, Australia*
  - Fatalities mostly in < 2 yr olds
  - Serious reactions at therapeutic doses in children > 2 yrs.
- *UK, serious in under 12s.*
  - Nasal decongestants (138, 64% 6 yrs and under)
  - Antihistamine containing preps (127, 72% < 6 yrs)
  - Expectorants (78, 70% < 6 yrs)
  - Antitussives (54)
  - For all except expectorants main suspected ADRs are CNS related
  - Expectorants, hypersensitivity

# ADR reports to regulatory authorities/pharmacovigilance centres

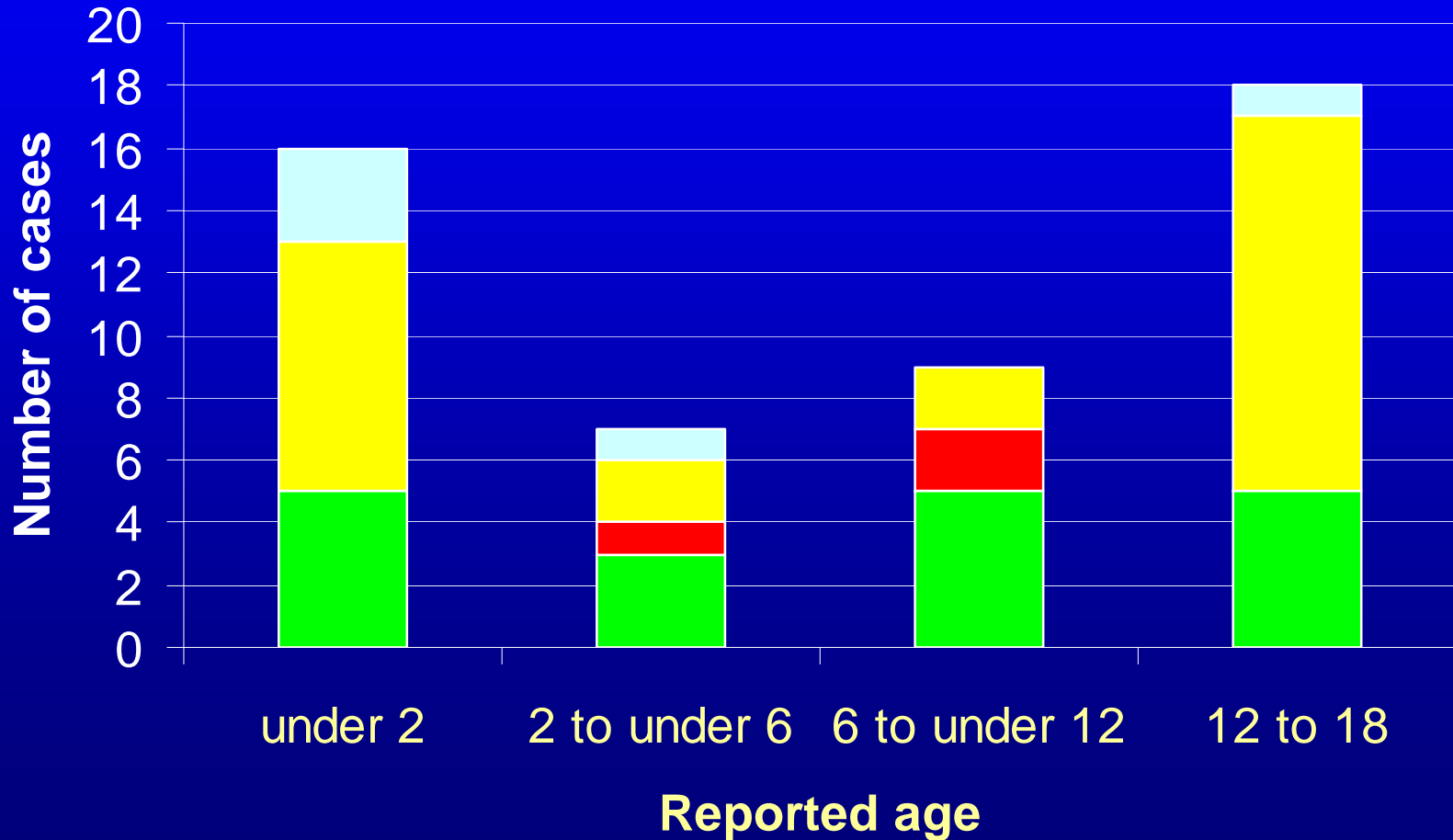
- Canada

- 111/145 reports (76%) for children < 6 yrs.
- Fatalities in under 2s only

# ADR reports to regulatory authorities/pharmacovigilance centres

- **US AERS database**
  - Decongestants: Fatal reports 9/54 for children 2-6 years.
  - Antihistamines Fatal 28/69 for 2-6s
  - ODs, 48% contributed to serious adverse events - antihistamines, antitussive, decongestant
  - Deaths and serious events - CNS, cardiac respiratory in therapeutic doses and overdoses.
  - Convulsions more common in > 2yrs and more common after therapeutic dose.
  - Serious cardiac and respiratory events more often after overdose.

# CARM data





# CARM (NZ) Data

44/306 reports for ages 18 yrs or below.

- Majority allergic or CNS adverse effects
- Less than a quarter are OD but CARM does not usually record ODs as ADRs.
- Seven patients hospitalised
- One life-threatening reaction (M6, phenylephrine OD /pulmonary oedema)
- No childhood deaths have been reported
- Only 2/8 serious reactions in  $\geq 2$  yr olds.

# Company ICSRs - Polaramine (dexchlorpheniramine), Demazin (chlorpheniramine/phenylephrine)

- Serious reports for 2 to 12 year olds submitted in Australia by Schering Plough, ? Australian reports
- 1993-2007. Polaramine, 25, Demazin 3.
- Probability assessed by RS.
- Polaramine. Nine identified as "probable".
  - Antimuscarinic and CNS effects inc hallucinations and decreased consciousness
  - Allergic reactions including laryngeal oedema
- Demazin Two "probable" -
  - ODs with tachycardia
  - Death, most likely cause pneumonia

# Company ICSRs - Bisolvon (bromhexine) - mucolytic

- ? 164 million exposures < 12 year olds based on sales of age appropriate products & 2 week courses. NB coughs and colds not main indication.
- Most ADR reports are of allergy, including anaphylaxis and skin reactions, and GI reactions. Most are listed as having "insufficient data".
- Similar number of ICSRs in 0-2 and >2 -6 year olds (81, 82) and three serious reports in each group. Fewer reports for >6-12 yr olds.
- Serious reports >2-6 yrs. Accidental O/D - diarrhoea; skin reaction/weight loss/tonsillitis; SJS.
- Overdose has caused skin and GI reactions, no significant toxicity or death.
- One report of SJS in >2 -6 yr olds and one of TEN in > 6 to 12 yr olds. Alternative explanations. Not supported by WHO data

# Health Canada Decision on OTC Cough & Cold Medicines

- When assessing risk Committee asked to consider -

*"The severity of the adverse effects and the likelihood of harm. "*

# Issues

- Fatal reports of ADRs or overdose very rare in > 2 yr olds
- Serious reports rare or very rare in > 2 yr olds
  - BUT widespread use!
- Anaphylaxis common to all the ingredients, cardiovascular and CNS reactions less likely with bromhexine and possibly guaifenesin
- Reasons for overdose of concern but accidental childhood ingestion may often involve preparations purchased for adults especially in NZ
- Will contraindication for < 6 yr olds lead to more dose errors if parents do give these medicines?

