

Efficacy of Cough and Cold OTC Drugs in Pediatric Populations

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Overview

- I. Clinical Evidence of Efficacy
 - Brompheniramine
 - Chlorpheniramine
 - Dextromethorphan
- II. Risks of Extrapolation
- III. Adverse Effects
- IV. Rational Therapeutics

Clinical Evidence

- **No more effective than placebo** in relief of cough and cold symptoms in children

Bromopheniramine	Diphenhydramine
Chlorpheniramine	Guaifenesin
Clemastine	Phenylephrine
Codeine	Phenylpropanolamine
Dextromethorphan	Salbutamol

Brompheniramine

- Prospective, randomized, double-blind, placebo-controlled
- 7-point Likert scale, sx improvement 2h after dose
- N=59, age range 6 mo – 6 yrs

Symptom	Drug	Placebo
Runny Nose (%)	50.6	57.5
Nasal Congestion (%)	48.8	50.6
Cough (%)	49.0	43.1
Asleep (%)	46.6	26.5

Chlorpheniramine

- Prospective, randomized, double-blind, placebo-controlled
- Symptom improvement at 3 days, rating scale: -1 (worse) to +3 (improved), pre-rx minus post-rx
- N = 143; age 1.5 mo to 5 yrs

Symptom (%)	Placebo	Drug
Nasal Discharge	61.7	75
Cough	39.6	27.6
Slight drowsiness	6.2	12.7
Sleepiness	2.1	8.6

Dextromethorphan

- Single dose study; 30 minutes before bed
- 7-point Likert scale (0 to 6)
- N = 100; ages 2-16.5 years

Symptom	DPH	DM	Placebo
Cough frequency	2	2	2
Cough bother child	2	1.8	2.1
Cough severity	2.1	2.1	2.1
Parent's sleep	1.5	1.8	1.5
Combination symptom score	9	10	10

Extrapolation Risks

- Pediatric research conducted under BPCA* has led to 133 labeling changes as of 8/07
- Drugs previously approved for adults have been found to be:
 - Ineffective: Sumatriptan for migraines, Tolterodine for bladder incontinence
 - Incorrectly dosed: Gabapentin for partial seizures, Benazepril for pediatric hypertension

*Best Pharmaceuticals for Children Act

Extrapolation Risks

- Many PK parameters change with developmental stage

Sotalol PK Parameters

Below 0.33 m² SA	Acts as β -blocker	More frequent QT prolongation
Above 0.33 m² SA	Acts as K-channel blocker	Increased plasma clearance and Vd

Extrapolation Risks

- Extrapolation also applies to clinical scenarios
 - Children have unpredictable clinical responses (fluoxetine, fluvoxamine trials)
 - Symptoms in a child may predict a different spectrum of disease than identical symptoms in an adult

Adverse Effects

- Numerous examples have revealed adverse effects unique to a pediatric population
 - Isotretinoin (Accutane) : increased bone demineralization
 - Topical pimecrolimus (Elidel) : increased infections, fever, and diarrhea
 - Propofol : increased mortality in multi-day continuous infusion

Next Steps: Rational Therapeutics

- Research on pathophysiology of the common cold: cytokines, chemokines, receptors
- Nasal spray vaccines and anti-viral drugs targeting rhinoviruses, parainfluenza
- ICAM-1 receptor antagonists