

Quality use of medicines: The patient with Acute Cough

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Surveys of family practitioners' prescribing habits have often found that patients presenting with respiratory tract infections are associated with increased levels of discomfort, as their expectations may well be in conflict with the therapeutic approaches proposed in evidence-based guidelines. For example a critical incident survey amongst practitioners in the North of England showed that they experienced the greatest discomfort when facing patients with respiratory diseases, musculo-skeletal problems or anxiety, or when contemplating the use of antibiotics, tranquillisers, hypnotics, or symptomatic remedies.¹ While decisions around antibiotic choice (or use at all) in respiratory tract infections are difficult enough, this paper tries to address what is often the second item on a prescription – the symptomatic relief of the cough itself. (*SA Fam Pract* 2003;45(8):22-24)

The reasons advanced by Flemish general practitioners for using antibiotics in such cases have recently been comprehensively described.² However, less has been written about the ambivalent attitude many authorities have towards "cough mixtures". Such ambivalence was intriguingly exposed when a South African pharmaceutical industry consultant opened the debate on the E-DRUG listserv in September 1997.³ At the time, the South African health authorities were trying to decide what to include in the Primary Care Essential Drug List. Some were leaning towards the use of a placebo/demulcent such as Simple Linctus BPC, rather than the ubiquitous diphenhydramine-containing products widely used at the time. Opinions were exchanged on the evidence base for the different products, as well as on the risk of dental caries with citric acid containing sugar solutions (such as the linctus mentioned). On these grounds, the Medicines Control Council deemed the product not registrable. Also raised was the spectre of increased antibiotic use if a cough mixture was not available to front-line prescribers. One contributor concluded "Are we being too rational by excluding

cough syrups from drug lists? We are treating patients with disease not just diseases, therefore I can justify comforting the patient if only to avoid them seeking "comfort" in unjustified chemicals at an unjustified cost". Can a review of the evidence help?

ANTITUSSIVES AND PROTUSSIVES

First, a matter of terminology has to be settled. Ten years ago, a review in *Drugs* argued that the treatment of cough could be divided into two major groups – therapy that "controls, prevents or eliminates cough" (i.e. antitussive), and therapy that "makes cough more effective" (i.e. protussive).⁴ It further divided antitussive therapy into specific (e.g. removing the cause by treating the infection, or removing a drug such as an ACE-inhibitor, treating the underlying gastro-oesophageal reflux or cardiac failure) and non-specific therapy (directed at the symptom). Critically, it noted that there was no evidence for the clinical effectiveness of any protussive preparations (such as expectorants) other than the aerosols used in chronic conditions such as cystic fibrosis. That

view persists to this day – a recent review in a *Family Practice* journal states "the pro-tussive idea is theoretical".⁵ That has interesting implications – for one, if the division between cough suppressants for "dry" coughs and expectorants for "wet" coughs has no basis, and substances commonly labelled as expectorants (such as ammonium chloride) are actually antitussive in action, then combinations previously considered potentially antagonistic and illogical might well be synergistic. But, are they effective? Assessing that evidence is complicated by the range of substances used. **Table 1** shows the major groups usually included in cough/cold preparations. That wide range is further complicated by the bewildering series of combinations on the market, which include antihistamines together with decongestants, antitussives and/or "expectorants", with or without analgesics.

EVIDENCE OF EFFICACY AND SAFETY

A recent systematic review has attempted to put this issue to rest. Schroeder and Fahey identified 328

Table I: Pharmacological classification of cough/cold preparations

| Classification | Putative action | Examples |
|----------------|---|---|
| Antitussives | centrally or peripherally-acting opioid derivatives; cough suppressants | codeine dextromethorphan |
| Expectorants | increased bronchial mucus secretions, easing movement by coughing or ciliary transport | guaifenesin ipecacuanha ammonium chloride |
| Mucolytics | decrease mucus viscosity, easing expulsion | bromhexine carboxymethylcysteine |
| Antihistamines | H ₁ receptor blockade, usually combined with sympathomimetic decongestants, to reduce mucus production | diphenhydramine brompheniramine doxylamine (often with ephedrine, phenylephrine, pseudoephedrine) |
| Demulcents | soothing action | sucrose |

potentially relevant randomised controlled trials (RCTs), but could find only 15 in adults and 6 in children that satisfied their inclusion criteria. The resultant analyses were published separately, and then combined as a Cochrane Review.^{6,7,8} The reasons cited for exclusion of trials from the analysis were illuminating: 23 were not in fact RCTs, 41 were not placebo-controlled, 109 were not testing an over-the-counter medicine, in 29 the cough was artificially induced, in 90 the condition was actually chronic cough (lasting more than 3 weeks) and in 15 no cough outcome was reported. Due to the range of methodologies used, the data could not be combined for analysis. In short, their findings were that:

- As an antitussive, codeine was no more effective than placebo, whereas dextromethorphan was favoured over placebo in one study in adults, but not in another. In paediatrics, no antitussives were more effective than placebo.
- Guaifenesin was rated by more adult participants in one trial as effective than was the case for placebo (75% vs. 31% in the control group), but no differences were seen in another trial. No trials of expectorants in children were included.
- In a single adult trial, a mucolytic was shown to reduce cough frequency and symptoms scores on days 4 and 8. In children, a single

trial favoured active treatment over placebo from days 4 to 10.

- Antihistamines were not shown to be effective in adults or children.
- Antihistamine-decongestant combinations were more effective than placebo in adults, but not in children.
- Two paediatric combination products (one with phenylpropanolamine, pheniramine, pyrilamine, dextromethorphan and ammonium chloride, the other combining phenylpropanolamine, dextromethorphan and glyceryl guaiacolate) were no more effective than placebo.

Each of these trials usually included minimal numbers of patients. The last mentioned, for example, showed a "satisfactory" response in 11/16 and 9/13 (both 69%) in the active groups and 8/14 (57%) in the placebo group. The authors also noted a further cause for concern – of the 21 studies reviewed, 9 were fully or partly supported by pharmaceutical companies. Six out of these 9 showed positive results, compared to 3/12 where no such support was reported. The authors concluded, cautiously given the paucity of data, that "there is no good evidence for or against the effectiveness of OTC cough medicines, and from the studies included in this review it remains unclear whether these medications are helpful for the treatment of acute cough". Each of the reviews published

separately also made the point that "even when trials had significant results, the effect sizes were small and of doubtful clinical relevance".

The BMJ publication (reviewing the adult trials) elicited a storm of letters and "rapid responses" on the journal's web site.⁹ Some attacked the conclusions, even though they had been cautiously stated: "the fact that people keep buying medicines is itself evidence"; "the predictable upshot of this is that the review showed no evidence of effect – not evidence of no effect, as many will have inferred" (from the medical advisors to a prominent pharmacy chain group). Another teacher/practitioner from the same group noted that there was no mention of pholcodine-containing products. The medical adviser to the National Health System's online advice service (NHS Direct Online) defended the careful statement included on that site, directed at adults: "Some people may find that a simple cough medicine helps to soothe a ticklish dry cough". A general practitioner (later revealed in fact to be a research fellow funded by the NHS) stated, "of course cough medicines don't work; but ... I shall continue encouraging patients to use them". Two prominent academics noted that over £100 million was spent annually on such products in the United Kingdom, and called for "funding for good quality research, not sensational extrapolation from inadequate data" (noting though that the extrapolation was the fault of the journal's editors, who highlighted the results in the "This Week in the BMJ" section). They, and an officer of the Consumer Healthcare Products Association, also pointed to a new meta-analysis published after the Cochrane Review selection process had been completed.

The meta-analysis in question was produced by staff of Proctor and Gamble's clinical development department.¹⁰ It combined data from 5 studies conducted at the company's Corporate Health Care Research Centre in Mumbai and 1 conducted in Durban, in a total of 710 patients. Of these 356 received a single dose of dextromethorphan 30mg (in either a liquid or capsule formulation) and 354 received a placebo. None of the studies was powered to show statistical significance, but all showed differences in efficacy

“directionally in favour of dextromethorphan”. The methodology used was novel – each study participant wore a recording apparatus capable of detecting and digitising data on the number of individual cough bouts, the components (sounds, or individual tussive blasts) within each bout, the rest periods between bouts (cough latency), the cough effort and “wetness” (based on sound and waveform) during a 3-hour post-dose period. Cough intensity was calculated as cough effort/total cough count. Statistically significant treatment differences were seen, based on the log least-squared means for the pooled data, in the number of cough bouts (12.7% fewer), cough components (13.4% fewer), cough effort (17.3% lower, based on the area under the curve of the cough acoustic power spectrum plot), and cough latency (17.3% greater cough-free periods). Individual time point analyses showed marked intra-individual variability over time. Interestingly, the liquid formulation produced greater differences in the first 60 minutes compared to the capsules (perhaps compounded by the fact that the liquid form contained menthol), and greater differences were also seen in those with dry rather than non-dry coughs.

However, while this meta-analysis was indeed not included in the Cochrane Review, three prior single-dose short-term cough relief studies from the same group were mentioned. Schroeder and Fahey questioned their relevance, noting that “more relevant outcomes for patients would be the effect after one day, three days or a week”.⁸ Not surprisingly, the Cochrane Review could find few data on safety (beyond the predictable sedation associated with older antihistamines). However, no controlled study will show the sort of problems that are encountered when such agents are used in practice, and contrary to the labelled instructions. Three such cases were reported in 2001.¹¹ In the first, an unspecified amount of a phenylpropanolamine/brompheniramine combination was suspected to have caused lethargy, bradycardia, tachypnoea and hypertension in a 36-month-old boy, who recovered with supportive therapy. In the second, a 35-month-old was admitted repeatedly with tachycardia and cardiomegaly. His parents denied giving

anything except Tylenol®, a paracetamol preparation, but when asked to produce the bottle brought in a Children’s Tylenol: Cold® preparation (containing chlorpheniramine, dextromethorphan and pseudoephedrine as well as paracetamol). The tachycardia slowly resolved and echocardiogram returned to normal by 2 weeks after discharge. The third, a 9-month-old boy, was given repeated doses of over-the-counter cough and cold preparations by his caregivers and suffered cardiopulmonary arrest. Post-mortem urine analysis showed paracetamol, pseudoephedrine, chlorpheniramine, dextromethorphan and phenylpropanolamine. Blood levels of all except paracetamol and chlorpheniramine were markedly elevated, and were considered to have contributed to his demise.

GUIDELINES

Given this evidence – questionable efficacy and potential toxicity (but with the caveat that absence of evidence is not evidence of absence) – how have professional organisations and guideline developers responded? The American Academy of Pediatrics is generally against the use of antitussives, preferring that patients and parents be educated about the lack of proven effects and the potential risks.¹² The Scottish Intercollegiate Guidelines Network (SIGN) hedges its bets with respect to adults: the guide states “cough suppression in LRTI may be justified for a non-productive irritating cough”, but includes as a “good practice point” the statement “there is no good evidence that cough mixtures work”.¹³

Work from the renowned Common Cold Centre in Cardiff shows how far we are from a definitive answer. Eccles has estimated that 85% of the effect of antitussives is due to a placebo effect (possibly mediated by endogenous opioid neurotransmitters), and has hypothesised that cough involves two pathways – one related to respiratory tract infections and not affected by codeine, and a reflex pathway associated with induced and chronic cough which is inhibited by codeine.^{14,15}

Cornford has shown that, for those who present to a medical practitioner with cough, this is not a trivial illness.¹⁶ The same group showed that mothers who presented feared that their child

was “going to die, usually because of choking on phlegm or vomit”.¹⁷ As with antibiotics, it seems the way forward should include careful patient education, in this case on the role of cough as an important protective mechanism and on the potential benefits and risks of antitussives. Where deemed necessary, a single agent form of dextromethorphan as a liquid or lozenge preparation may perhaps be recommended. If over-the-counter purchases are to be recommended, perhaps demulcents do no less than any of the others. Finally, perhaps the Medicines Control Council should consider the registration status (or at least the claims made by the manufacturers) of those products for which little or no efficacy data exists – the work of the Bristol group, responsible for the Cochrane Review, has prompted the Irish Medicines Board to do just that.¹⁸ As Paul Spivey wrote on E-DRUG, they might well be “unjustified chemicals at an unjustified cost”. □

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