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Effects of safety warnings on prescription rates of cough and cold medicines in children below 2 years of age

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Cough and cold medicines are frequently used in children to treat upper respiratory tract infections without solid proof of benefits.
- Safety issues have been raised about the use of these drugs in young children.
- In 2007 international warnings were issued advising against use of these drugs in young children.

WHAT THIS STUDY ADDS

- Cough and cold medicines prescribing by primary care physicians has not really been influenced by international warnings in the Netherlands, where no additional national warnings were made and only partially in Italy.
- A concerted action should be taken in Europe to advise strongly against the OTC use and prescription of cough and cold medicines in young children.

AIM

The aim of the study was to assess the influence of national and international warnings on the prescription rates of cough and cold medicines (CCMs) in the youngest children (<2 years) in the Netherlands and Italy.

METHODS

Analysis of outpatient electronic medical records of children <2 years in Italy and the Netherlands was carried out. Age and country specific prescription prevalence rates were calculated for the period 2005–08. Comparisons of prescription rates in 2005 (pre) and 2008 (post) warnings were done by means of a chi-square test.

RESULTS

The cohort consisted of 99 176 children <2 years of age. After international warnings, overall prescription rates for CCMs decreased slightly from 83 to 77/1000 person years ($P = 0.05$) in Italy and increased in the Netherlands from 74 to 92/1000 children per year. Despite the international warnings, prescription rates for nasal sympathomimetics and opium alkaloids increased in the Netherlands ($P < 0.01$). In Italy a significant decrease in the prescription rates of opium alkaloids and other cough suppressants ($P < 0.01$) was observed, and also a significant reduction in use of combinations of nasal sympathomimetics.

CONCLUSION

Despite the international safety warnings and negative benefit-risk profiles, prescription rates of cough and cold medicines remain substantial and were hardly affected by the warnings, especially in the Netherlands where no warning was issued. The hazards of use of these medicines in young children should be explicitly stipulated by the European Medicines Agency and all national agencies, in order to increase awareness amongst physicians and caretakers and reduce heterogeneity across the EU.

Introduction

Cough and cold medicines (CCMs) are frequently used to treat upper respiratory tract symptoms in children. This group of medicines includes expectorants, mucolytics, opium alkaloids (for cough), nasal sympathomimetics and anti-histamines. CCMs carry a risk of serious and potentially life-threatening adverse events, such as cardiac arrhythmias, depressed levels of consciousness and encephalopathy, and should be avoided in the very young [1].

As a result of these safety issues, in 2007 various regulatory actions were taken in many countries: in the United States, the Food and Drug Administration (FDA) issued a recommendation advising parents and caregivers not to use these drugs in children younger than 2 years of age [2]; in the United Kingdom, the Medicine and Healthcare Products Regulatory Agency (MHRA) advised against the use of many CCMs in children under the age of 6 years [3] and Health Canada required manufacturers to re-label certain over-the-counter (OTC) CCMs to indicate that these should not be used in children under the age of 6 years [4]. In Italy a warning was issued in September 2007 regarding only the use of nasal sympathomimetics in children <12 years. However in the Netherlands and many other countries, no national warning was issued. The safety concerns on the use of CCMs in young children, and the regulatory actions, also received a lot of attention from the scientific community. Sharfstein *et al*. published an important paper in the New England Journal of Medicine which was followed by publications in many lay press journals and media attention in most countries [1].

Most of the utilization data that have been published focus on OTC use of CCMs, as this is the major market in the USA [5–10]. Although CCMs can be bought as OTC in many countries, they are also regularly prescribed by physicians, especially when being re-imbursed. Previous studies have shown that prescription rates of, for example, antidepressants and antipsychotics drop after regulatory warnings [11–13]. However, to our knowledge, no studies have been performed that evaluate the effect of regulatory warnings on CCMs prescription rates. We aimed to investigate the extent of use and to study the effects of the warnings on the prescription rates of CCMs to children under the age of 2 years (since this is the group included in all international warnings) in the Netherlands and Italy, two countries with different types of direct national warnings (the Netherlands none, and Italy only on nasal sympathomimetics).

Methods

Data collection

Data were obtained from general practice medical record databases in two countries and were extracted and elaborated according to a common protocol. Databases comprised the Pedianet database in Italy [14] and the Integrated Primary Care Information (IPCI) database in the Netherlands [15]. These databases include complete automated medical records of primary care physicians. The patient population in each database is representative of the respective Dutch and Italian population regarding age and gender. The electronic records contain anonymous and coded information on patient demographics, symptoms and diagnoses, referrals, clinical findings, laboratory assessments, drug prescriptions and hospitalizations. Details of these databases regarding their paediatric data are described elsewhere [16].

Study population

The study period was from 1 January 2005 to 31 December 2008. The study population in each country consisted of all children aged 0–2 years (up to 24 months). Each patient was followed from start of the study period or date of registration with the primary care practice (whichever was latest), until the patient left the practice or end of the study period (whichever was earliest).

Classification of prescriptions

Cough and cold medicines of interest comprised the following medicines: expectorants (ATC R05CA: althea root, thyme, combinations containing promethazine, oxomemazine, terpenes, guaiacol and eucalyptus), mucolytics (ATC R05CB: ambroxol, bromhexine, acetylcysteine, carbocisteine, sobrerol, erdosteine, dornase alpha), opium alkaloids and derivatives (ATC R05DA: codeine, dextromethorphan, dihydrocodeine, noscapine and opium combinations containing pentetrazol, pseudoephedrine, triprolidine or codeine), other cough suppressants (ATC R05DB: pentoxyverine, levodropropizine, clobutinol, butamirate, dropropizine, cloperastine and combinations containing pentoxyverine, terpenes or thyme), nasal sympathomimetics (ATC R01AA: xylometazoline, oxymetazoline, phenylephrine, naphazoline) and combinations of nasal sympathomimetics (ATC R01AB). These drug classes were extracted from the databases using the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system [17].

Statistical analysis

Annual prescription rates [users per 1000 person years (PY)] of CCMs were estimated by counting the number of children being prescribed each drug or drug class divided by the number of person years attributed, categorized by calendar year, age and country. Prescription rates can be interpreted as the number of children per 1000 children who get a specific drug (class) prescribed in 1 year. Because we used annual prescription rates, a child who uses one drug (class) multiple times in 1 year will be counted only once for that year. To inspect seasonal variability monthly rates were calculated by dividing the number of users per month by the person months attributed.

To study the effect of the international warnings in 2007 on prescription rates, we compared prescription rates between 2005 and 2008 for each individual drug and drug class by a chi-square test. *P* values below 0.05 were considered to be significant.

Results

Patient characteristics

Our population of 99 176 children under the age of 2 years generated 110 169 person years of follow-up (Table 1). The overall distribution of children per country was fairly equal, 52% of the patients were from Italy and 48% from the Netherlands.

Prescription rates of cough and cold medicines

In the Netherlands CCMs prescription rates increased significantly between 2005 and 2008 from 74 to 92/1000 PY ($P < 0.01$), but decreased slightly from 83 to 77/1000 PY ($P = 0.05$) in Italy (Figure 1). In both countries a strong seasonal prescription pattern could be observed, with peaks during winter time (Figure 2). The seasonal patterns of CCMs prescription rates were similar before and after the international warnings in Italy and the Netherlands.

When looking at classes of CCMs, different patterns were observed, both in terms of preferred medicines between countries and changes in annual prescription rates. Expectorants were mostly prescribed in the Netherlands, and rates decreased significantly from 10.8 to 4.3/1000 PY ($P < 0.01$) (Table 2), mostly because of a decrease in prescription of both thyme syrup ($P < 0.01$) and combination products ($P < 0.01$) (Table 3). In Italy the only expectorants prescribed were combination products, and prescription rates for these increased slightly.

Mucolytics were 10 times more often prescribed in Italy than in the Netherlands. In both countries, overall rates did not change before and after the warning, but small changes occurred in prescription of individual products. In particular prescription rates of sobrerol increased in Italy and dornase alpha in the Netherlands (Tables 2 and 3).

Opium alkaloids and derivatives for cough suppression were most frequently prescribed in the Netherlands and prescription rates even tripled between 2005 and 2008 from 4.2 to 13.4/1000 PY ($P < 0.01$). This increase was due to a substantial rise in prescription rates of noscapine. In contrast, in Italy prescription rates of opium alkaloids dropped by half from 7.4 in 2005 to 3.6/1000 PY in 2008 ($P < 0.01$). This decrease was seen for all products in this class (Tables 2 and 3). Prescription rates for other (non-opioid) cough suppressants were highest in Italy, and this was mostly accounted for by levodropropizine. Rates

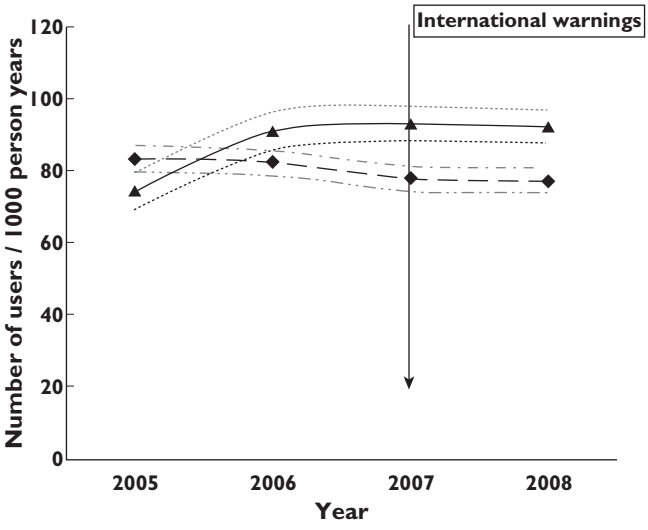

Figure 1

Prescription rates of cough and cold medicines by database and year with 95% confidence intervals. IPCI Dutch database, Pedianet Italian database. IPCI (—▲—); IPCI 95% CI upper limit (·····); IPCI 95% CI lower limit (·····); Pedianet (—◆—); Pedianet 95% CI upper limit (– – –); Pedianet 95% CI lower limit (— · · —)

Table 1

Number of children in the study population and persontime by gender and calendar year

	Italy			The Netherlands		
Patient characteristics	Children†	PY	GP practices*	Children†	PY	GP practices*
Females	24 532 (48%)	33 862		23 406 (49%)	19 741	
Males	26 890 (52%)	37 002		24 348 (51%)	19 564	
2005	19 070	16 338	158	11 331	8 422	134
2006	19 424	18 780	176	12 189	8 340	136
2007	18 611	18 234	160	13 128	10 845	138
2008	17 596	17 512	170	13 219	11 698	138
Total	51 422	70 864		47 754	39 305	

*The number of contributing general practitioner's practices to the study population. †The number of children in various years does not add up to the total since one child can contribute in more than 1 year during the study period. PY, person years.

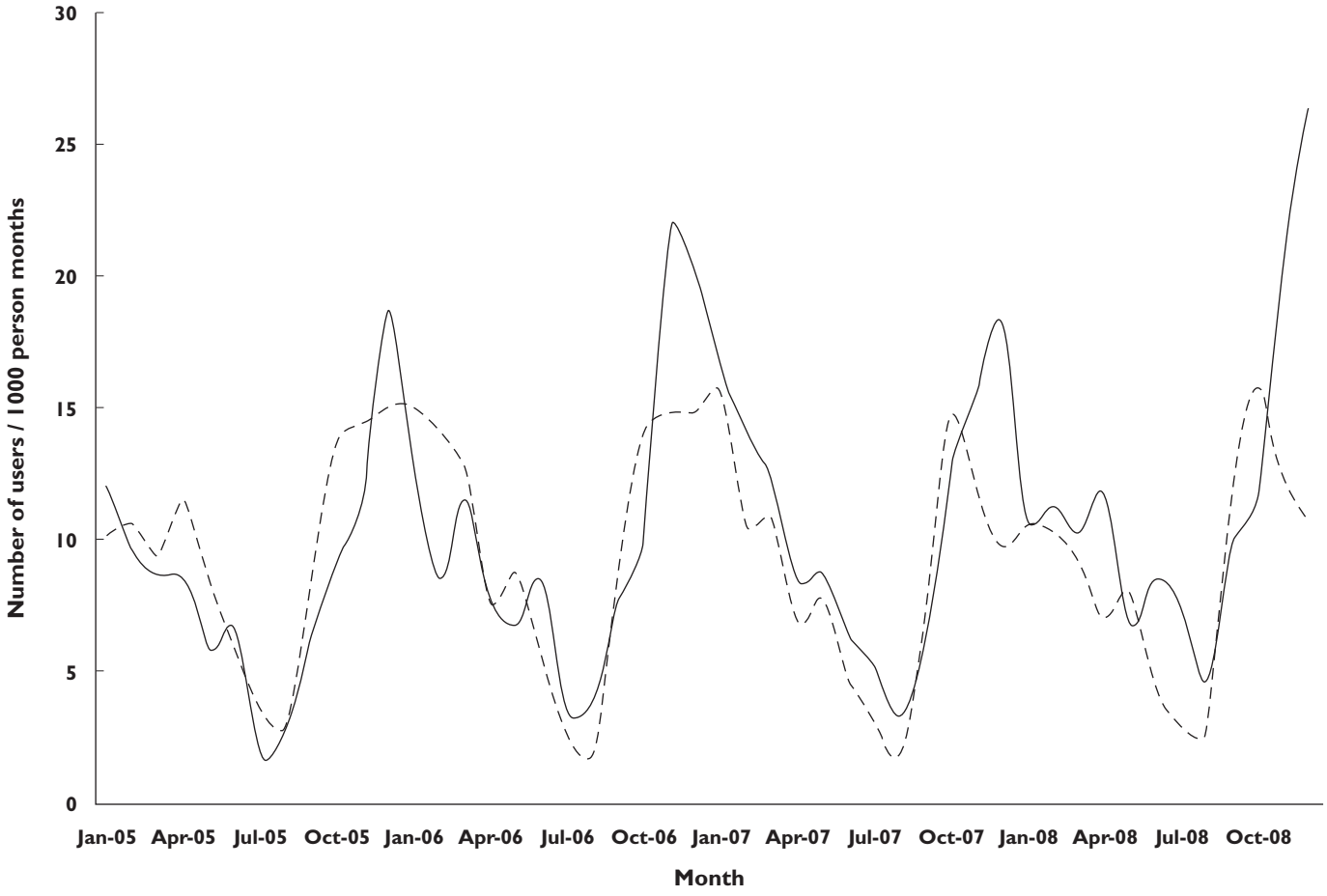

Figure 2

Prescription rates of cough and cold medicines by database and calendar month. IPCI Dutch database, Pedianet Italian database. IPCI (——); Pedianet (– – –)

Table 2

Prescription rates of cough and cold medicines per 1000 person years by year and country

	CCMs		Cough relievers				Cough suppressants				Nasal decongestants			
	Overall		Expectorants		Mucolytics		Opium alkaloids and derivatives		Other		Sympathomimetics		Sympathomimetic combinations	
Year	NL	IT	NL	IT	NL	IT	NL	IT	NL	IT	NL	IT	NL	IT
2005	74	83	10.8	4.1	6.6	54	4.2	7.4	7.7	21	51	0.9	–	7.3
2006	91	82	9.4	5.6	7.1	56	6.4	5.4	7.2	22	67	1.1	–	4.6
2007	93	78	6.8	5.2	8.6	58	10.9	3.6	9.7	17	70	0.3	–	1.4
2008	92	77	4.3	5.0	5.2	58	13.4	3.6	6.2	16	73	0.1	–	0.3
Overall	*88**	*79*	*7.1**	*5.0*	*6.8*	*57*	*9.3**	*5.0**	*7.7*	*19**	*66**	*0.6**	–	*3.3**

*Significant change between 2005 and 2008 ($P < 0.05$). IT, Italy; NL, the Netherlands. –, not available in NL.

decreased by one third after the warning ($P < 0.01$, Tables 2 and 3). In the Netherlands, use of other cough suppressants did not change significantly.

Single product nasal sympathomimetics (mostly xylometazoline) were primarily prescribed in the Netherlands, and prescription rates increased significantly from 51 in 2005 to 73/1000 PY in 2008, mostly due to use of xylometazoline ($P < 0.01$) (Table 2). In Italy, xylometazoline was hardly prescribed even before the warning, and prescription rates decreased to almost 0 in 2008. On the other hand, combinations of nasal sympathomimetics were only prescribed in Italy, and a strong effect of the warning was seen on their prescription rates (from 7.3 in 2005 to 0.3/1000 PY in 2008, $P < 0.01$). Medicines

Table 3

Pre- and post-warning prescription rates per 1000 person years of individual cough and cold medicines

Class of CCM	The Netherlands	2005	2008	*P* value	Italy	2005	2008	*P* value
Expectorants	Combinations*	4.3	1.7	<0.01	Combinations‡	4.1	5.0	0.24
	Thyme syrup	14.8	0.8	<0.01				
	Althea root	0	0.08	0.40				
Mucolytics	Bromhexine	4.4	3.2	0.16	Ambroxol	17.6	19.8	0.13
	Acetylcysteine	2.0	2.0	0.93	Sobrerol	16.0	20.2	<0.01
	Carbocisteine	0.2	0	0.47	Carbocisteine	13.4	14.0	0.65
	Dornase alpha	0	.08	0.40	Bromhexine	9.7	8.2	0.14
Opium alkaloids and derivatives	Noscapine	3.7	14.1	<0.01	Dextromethorphan	3.8	1.8	<0.01
	Codeine	0.8	0.4	0.88	Codeine	2.3	0.9	<0.01
					Combinations§	0.7	0.2	0.01
Other cough suppressants	Pentoxyverine	7.4	6.2	0.30	Levodropropizine	14.8	10.8	<0.01
	Combinations†	0.6	0	0.28	Cloperastine	5.6	5.0	0.40
					Clobutinol	0.2	0	0.42
Nasal sympathomimetics	Xylometazoline	51	73	<0.01	Phenylephrine	0.8	0.1	<0.01
	Oxymetazoline	0.1	0.4	0.21	Naphazoline	0.1	0	0.48
Combinations of nasal sympathomimetics	–				Ephedrine based	4.6	0.2	<0.01
					Tuaminoheptane based	2.9	0.1	<0.01

*Combinations containing promethazine, oxomemazine, guaiacol, ipecacuanha. †Combinations containing pentoxyverine, terpenes, thyme. ‡Combinations containing terpenes, eucalyptus, guaiacol, thyme. §Combinations containing pentetrazol, dihydrocodeine, codeine, dextromethorphan, pseudoephedrine, triprolidine. –, not available in the Netherlands.

prescribed in this class were combinations with ephedrine or tuaminoheptane.

Discussion

This paper provides information on the effects of national and international warnings on rates of prescriptions of cough and cold medicines in a country with and a country without additional national warnings. The formal regulatory review of OTC drugs, including CCMs, started in 1972 in the United States [18]. At that time, most OTC CCMs were generally recognized as safe and effective. Until recently CCMs received little attention regarding their safety and efficacy in children. In 2007, this changed dramatically by a citizen petition submitted to the FDA, raising significant concerns about the safety and efficacy of CCMs in children under the age of 6 years. This petition resulted in a public health advisory by the FDA, recommending that CCMs should not be used in children under 2 years of age because of the risk of serious and life-threatening effects [2]. The FDA warning was followed by other countries issuing warnings and several literature publications.

Despite the international warnings and important publications in high impact journals and lay press advising against the use of CCMs in young children, overall prescription rates for CCMs increased in the Netherlands, where no national warning was issued. Use of opium alkaloids and nasal sympathomimetics increased significantly, although these drugs are contra-indicated in young children [19]. In Italy, where a specific warning was issued by the Agenzia Italiana del Farmaco only against the use of nasal sympathomimetics, a significant reduction in use of nasal sympathomimetics was seen and also a decrease in use of cough suppressants (opioids and non-opioids).

Although the warnings did not show a considerable impact on the overall prescription rates in the Netherlands, there were shifts in the use of individual medicines. Rates for expectorant combinations decreased (comprising of promethazine and oxomemazine), whereas the prescription rates for noscapine, an opium alkaloid, increased substantially. Substantial evidence of adverse events related to the use of promethazine and oxomemazine in children exists [1, 20]. There are no studies evaluating the safety of noscapine in children, and no safety issues have been raised so far on the use of these drugs in young children. The Dutch GP society recommends noscapine for the symptomatic treatment of cough in young children [21]. This change from expectorant combinations to noscapine may be seen as a favourable trend although safety of noscapine in these young children should be further investigated. The observed increase in prescription rates of nasal sympathomimetics in the Netherlands is of high concern, since these drugs may cause serious adverse events such as lethargy, tachycardia, convulsions and even coma [22–26]. Furthermore, a recent Cochrane review concluded that insufficient data are available on the safety and efficacy of many nasal decongestants in children. Therefore, these drugs are not recommended for use in children <12 years of age [27].

In Italy, safety warnings were issued in September 2007 advising against the use of nasal sympathomimetics in children <12 years. Prescription rates of these drugs reduced significantly after the warning.

Our data show that CCMs are still prescribed to very young children, and prescription rates were hardly influenced by the international safety warnings, especially in the Netherlands where no national regulatory action was taken. In Italy we could observe positive effects from the safety warnings in some drug classes. Overall however, more action should be taken since use of these drugs in the very young may raise safety issues, and there is no evidence of efficacy [20, 28–30]. The few studies that evaluated the efficacy of CCMs in children with cough and cold found no significant benefit in symptomatic relief when compared with placebo [31–35]. Besides a lack of efficacy, CCMs are more prone to dosing errors. Variations in liquid CCMs dosing with spoons can be as much as 20%, leading to a higher risk of adverse events [36]. A recent study investigating therapeutic errors in children found that 23% of the dosing errors were related to use of CCMs [37]. Another study exploring paediatric fatalities associated with OTC CCMs use concluded that 85% of the fatalities were associated with an overdose of CCMs, mainly in children under the age of 2 years [38].

Not only are the country specific differences of the international warnings on the prescription rates of CCMs of interest but also the differences in the types of CCMs that are prescribed. In Italy sympathomimetics are hardly used but very commonly prescribed in the Netherlands, whereas in the Netherlands use of mucolytics is very low, but frequently prescribed in Italy. This is probably due to country specific guidelines on the symptomatic relief of cough and cold.

Many of the CCMs, which are still prescribed as seen in this study, are contraindicated in children younger than 6 years in the United Kingdom and Canada and younger than 2 years in the US [2, 3, 39]. This makes prescription by primary care physicians to young children even more alarming. To minimize the use of CCMs in children, these drugs should no longer be available OTC. Carer and physician education about the self-limiting nature of coughs and colds, the lack of efficacy and the risks associated with these drugs is needed [1, 40].

As for all observational research, our data have limitations. First of all, since we used primary care prescription data, we did not capture OTC use of these drugs and had no data on actual intake. However, our aim was to analyze prescription rates of CCMs by primary care physicians as these health professionals are approached directly by regulators/inspectorates. Furthermore, we could not compare our results with pre- and post-warning prescription rates in countries where more extensive warnings have been given, since no data have been published on this subject.

A major strength of our study is the fact that we captured a large number of children in two different databases across Europe, resulting in a high generalizability of the study population and our study findings.

To conclude, our results show that despite international warnings, a negative safety profile and lack of efficacy data, CCMs are still prescribed to young children in primary care in Italy and the Netherlands, and in the latter country rates even increased. Also, CCMs were prescribed that contain specific active ingredients proven to be most harmful in young children. Two lessons can be learned from this study. First of all, primary care physicians should be more aware of the harm and lack of efficacy of these drugs and should not prescribe them to young children. Secondly, there is heterogeneity in warnings across countries in the EU, which creates inequality. In order to increase awareness among physicians and caretakers and to allow for consistent warnings, the hazards of use of these medicines have to be explicitly stipulated by the European Medicines Agency. A concerted action is needed in Europe to advise against the use and prescription of cough and cold medicines to young children.

Conflicts of Interest

None of the authors has a conflict of interest related to the topic of this paper. The principal investigator had full access to all of the data in the study and takes responsibility for their integrity and the accuracy of the data analysis. KV has been involved as project leader in analyses contracted by various pharmaceutical companies and received unconditional research grants from Pfizer, Yamanouchi and Boehringer-Ingelheim; none of which are related to the subject of this study. GP is director of a company who has received grants for conduct of research from Merck and Pfizer. MS has received travel reimbursement from AstraZeneca and as head of a research unit receives unconditional research grants from Pfizer, Lilley and Altana. She has been a consultant for Pfizer and Novartis.

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