Clinical symptoms and 'off-label' prescribing in children with asthma

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ABSTRACT

A UK-wide database of structured asthma review consultations was used to investigate the prevalence of 'off-label' anti-asthma prescriptions in relationship to clinical symptoms of asthma control. The 1050 children (6.1%) aged 16 years or under issued with an off-label prescription reported more nighttime, daytime and activity asthma symptoms, and used more short-acting β_2-agonist medication than their peers. Off-label prescribing for children with asthma in UK primary care is associated with worse levels of self-reported asthma control.

Keywords

asthma; child health; drug labeling; family practice; prescriptions.

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INTRODUCTION

One in 10 people in the UK will receive an anti-asthma prescription at some stage in their childhood.[1] Asthma management guidelines give specific advice on medications and associated doses to be used for children, but make allowances for consultant paediatricians to increase these doses.[2] 'Off-label' prescribing in hospitals is a commonly accepted practice,[3] as the advantages of disease control out-weigh the theoretical risk of harm.[4]

The majority of patients with asthma are managed exclusively within general practice. Primary care health professionals have developed the skills to manage moderate-to-severe asthma, and are familiar with prescribing a wide range of medication products and medication.[5] GPs face the same off-label prescribing dilemma, with the National Service Framework for Children, Young People and Maternity Services[6] suggesting that prescribing of unlicensed and off-label medications should be considered to manage disease, but only where local standards and arrangements are in place to oversee and monitor the process.

Off-label prescribing is expanding in primary care, with reported levels between 13–29%.[7–10] There has been little work relating off-label prescribing to clinical symptoms for large populations. The clinical circumstances in which off-label prescribing occurs need to be investigated to inform the debate over the use of off-label medication.

METHOD

General practices throughout the UK were invited to participate in an audit process. Practices invited patients receiving preventative asthma medication for review, as recommended by guidelines for asthma management.[2] The structured clinical review was guided by and recorded using specially designed software based on a well-established standardised recording tool.[11] Practices recorded review consultations for varying periods of time between August 2001 and December 2004.

The review addressed inhaler technique, self-management plan use, compliance, education, and therapeutic change. Data recorded were presence of symptoms, level of asthma control, health service

utilisation and medication. Data from patients who gave written consent were anonymised and returned to the University of Dundee for analysis and preparation of audit feedback to practices.

The *British National Formulary* (March 2003) was searched for age-related restrictions for asthma medications. An off-label prescription was identified as a formulation not licensed for use in children, not licensed for use in a particular age group, or with a specific dosage not licensed for use. The database was analysed and all recorded consultations for patients aged 16 years and under were extracted. Medication use at each consultation was examined and patients receiving an off-label prescription were identified.

Details of the first recorded consultation for each patient were extracted: age, sex, symptom scores at night, daytime and during activity, daily use of short-acting β_2-agonists, recorded compliance, and poor inhaler technique.

Statistical analysis

To test for differences in proportions for patients in each category of interest, χ^2 tests were performed and presented as the χ^2 test statistic, degrees of freedom and *P*-value. The χ^2 test for trend was reported when it was significant.

RESULTS

A total of 1188 practices returned data on 17 163 children aged 16 years or under; 9800 (57.1%) were male. Of these children 1050 (6.1%) received an off-label prescription, 325 (1.9%) received drugs not licensed for their age group, and 767 (4.5%) received drugs at a higher than recommended dosage. Anti-cholinergics, oral β_2-agonists, long-acting β_2-agonists, inhaled corticosteroids and combinations of long-acting β_2-agonists and inhaled corticosteroids, were prescribed outside their licensed age groups, and at doses different from those recommended.

Younger children were more likely to have an off-label prescription (Table 1). The sex distribution was unremarkable.

Off-label prescriptions were associated with increases in the level of symptoms at nighttime, daytime and during activity, and reported daily short-acting β_2-agonist use, but not with compliance or inhaler technique (Table 2).

DISCUSSION

This study suggests an association among off-label prescribing, higher levels of symptoms, and more frequent use of short-acting β_2-agonists. GPs appear to be prescribing off-label medication to help manage more poorly controlled asthma in children.

How this fits in

Previous research has shown high levels of 'off-label' prescribing to hospital-based paediatric populations. More recent studies have shown similar findings in community settings. This study of patients attending practices throughout the UK shows a relationship between instances of off-label prescribing and increased symptoms of asthma and reliever medication use.

Table 1. Distribution of sex and age by off-label prescribing.

	Children with licensed prescribing (%)	Off-label prescription (%)	χ^2 test for trend[a] (*P*-value)
Total number of children	16 113	1050	
Males	9198 (57.1)	602 (57.3)	0.016
Females	6915 (42.9)	448 (42.7)	(0.900)
Age in years			
0–2	452 (2.8)	89 (8.5)	
3–5	2190 (13.6)	266 (25.3)	81.885
6–11	7867 (48.5)	353 (33.5)	(<0.001)
12–16	5548 (34.5)	340 (32.4)	

Fifty-eight patients (two with 'off-label' prescriptions) did not have a valid age recorded.
[a]*Degrees of freedom = 1.*

Table 2. Symptom scores, short acting β_2-agonist use, compliance and inhaler technique by off-label prescribing characteristics.

	Children with licensed prescribing (%)	Off-label prescription (%)	χ^2 test for trend[a] (*P*-value)
Total number of children	16 113	1050	
Nighttime symptom score[b]			
0 — None	8959 (55.6)	403 (38.4)	
1 — 1–2 per month	2510 (15.6)	202 (19.2)	126.705
2 — 1–2 per week	2377 (14.8)	196 (18.7)	(<0.001)
3 — Daily	2267 (14.1)	249 (23.7)	
Daytime symptom score[b]			
0 — None	6649 (41.3)	301 (28.7)	
1 — 1–2 per month	3382 (21.0)	208 (19.8)	105.346
2 — 1–2 per week	3236 (20.1)	239 (22.8)	(<0.001)
3 — Daily	2846 (17.7)	302 (28.8)	
Activity symptom score[b]			
0 — Rarely	6925 (43.0)	347 (33.0)	
1 — Sport	5919 (36.7)	361 (34.4)	87.082
2 — Active play	2876 (17.8)	293 (27.9)	(<0.001)
3 — Walking on flat	393 (2.4)	49 (4.7)	
Daily short acting β_2-agonist use[b]			
0	9536 (59.2)	467 (44.5)	
1	2014 (12.5)	132 (12.6)	93.105
2	2319 (14.4)	221 (21.0)	(<0.001)
>3	2244 (13.9)	230 (21.9)	
Poor compliance as assessed by the reviewer	3200 (19.9)	208 (19.8)	1.518 (0.218)
Poor inhaler technique as observed at the review	1735 (10.8)	109 (10.4)	0.116 (0.733)

[a]*Degrees of freedom = 1.* [b]*Significantly higher for patients who received an off-label prescription.*

However, this study cannot comment on whether local standards and monitoring arrangements are established as recommended by the National Service Framework for Children, Young People and Maternity Services.[6] It is important to state that all therapeutic decisions involve risk–benefit analysis, not just those involving off-label medications.

The study prevalence of 6% is lower than the figure of 26% reported by Ekins-Daukes *et al*,[7] but is similar in that high dosages are the main cause of off-label prescribing in anti-asthma medications. Although prevalence estimates vary between studies, the same conclusion is drawn; all clinicians working in primary care will encounter the dilemma of seeking optimum control within the constraints of prescribing guidelines.

Although based on 'real life' clinical practice the current study has limitations because the clinicians who chose to participate in an electronic review and feedback service are by definition atypical. However, the children under their care are likely to be representative of children with asthma in the UK. It may be that trained or 'asthma interested' GPs are less willing to advocate off-label prescribing for uncontrolled asthma effecting the rate. However, the converse might equally be true. Further research including a qualitative examination of views and attitudes to off-label prescribing among GPs could be helpful in determining why the decision to prescribe is made.

This study suggests that off-label prescribing in children with asthma occurs in those with the poorest asthma control. Each individual case requires a prescribing decision which involves prescriber and patient in a risk–benefit analysis. Further work is required to fully understand this decision making process.

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Ethics committee

All practices and individual patients gave signed consent for transfer and use of anonymised data. Ethical approval for the project was granted by the Tayside Medical Research Ethics Committee (242/00)

Competing interests

The authors have all been in receipt of research grants and speaker fees from several of the manufacturers of anti-asthma medications but have no direct financial interest in the 'off-label' debate

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