
Monograph:
Stevenson, M.D., Richards, R.G. and Beard, S.M. (1999) The role of antileukotrienes in the treatment of chronic asthma. Other. Guidance Notes for Purchasers (99/01). Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield , Sheffield. ISSN 1900733315

April 1999

THE ROLE OF ANTILEUKOTRIENES IN THE TREATMENT OF CHRONIC ASTHMA

M D Stevenson
R G Richards
S M Beard

Series Editor: Nick Payne

Trent Institute for Health Services Research
Universities of Leicester, Nottingham and Sheffield

GUIDANCE NOTE FOR PURCHASERS 99/01

InterDEC No: 01/1999

Published by the Trent Institute for Health Services Research

ISBN 1 900 733 31 5

Referencing information:

Stevenson MD, Richards RG, Beard SM. *The Role of Antileukotrienes in the Treatment of Chronic Asthma.* Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield, 1999. Guidance Note for Purchasers: 99/01.

Further copies of this document are available (price £15.00) from:-

Information Resources
Trent Institute for Health Services Research
Regent Court
30 Regent Street
SHEFFIELD S1 4DA

Tel 0114 222 0703
Fax 0114 272 4095
E-mail scharrlib@sheffield.ac.uk

Conflict of Interest None of the authors of this document has any financial interests in the drug or product being evaluated here.

AUTHORS

Dr M D Stevenson is an Operational Research Analyst at The School of Health and Related Research (ScHARR), The University of Sheffield.

Dr R G Richards is a Consultant in Public Health Medicine, North Nottinghamshire Health Authority.

Mr S M Beard is a Senior Operational Research Analyst at The School of Health and Related Research (ScHARR), The University of Sheffield.

ACKNOWLEDGEMENTS

The authors wish to thank Professor M Silverman, Professor of Child Health, Leicester Royal Infirmary, for his assistance with the preparation of this Guidance Note.

ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking HSR;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Dr M E Dewey (Acting) (Nottingham); and
Professor M Clarke (Leicester).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

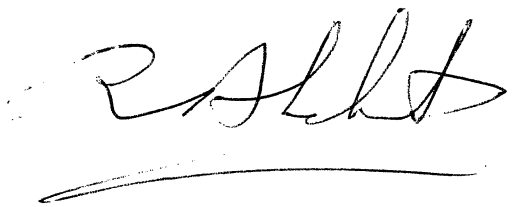
A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority and Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterTASC, with units in other regions. These are: The Wessex Institute for Health Research and Development and The University of Birmingham Department of Public Health and Epidemiology.



Professor R L Akehurst,
Chairman, Trent Working Group on Acute Purchasing

ABBREVIATIONS

A&E	Accident & Emergency
ALTs	Antileukotrienes
BTS	British Thoracic Society
COPD	Chronic Obstructive Pulmonary Disease
FEV_1	Forced Expiratory Volume in 1 second
HTAs	Health Technology Assessments
ONS	Office of National Statistics
PACT	Prescribing Analysis and Costs
PEFR	Peak Expiratory Flow Rate
PN	Practice Nurse
QALY	Quality Adjusted Life Year

CONTENTS

LIST OF TABLES AND FIGURES

Page

EXECUTIVE SUMMARY

Chronic asthma is a common disease, affecting up to 12% of the population, although only 6.7% receive treatment. It is the cause of considerable morbidity and mortality resulting in 1,358 deaths in England in 1997. It is an inflammatory disease of the lower airways caused by a variety of intrinsic and extrinsic factors.

Current management is typically by combinations of inhaled or oral preparations in increasing amounts as the disease worsens and is governed by guidelines from the British Thoracic Society (BTS). Inhaled corticosteroids are the mainstay of preventive treatment in the UK.

Leukotrienes are one of the mediators in the inflammatory response and a new class of drugs, the antileukotrienes, has been developed to block that inflammatory biochemical pathway. Early clinical trials have shown two UK licensed antileukotrienes, montelukast and zafirlukast, and two as yet unlicensed antileukotrienes, pranlukast and zileuton, to be better than placebo at improving lung function and asthma symptoms. More recent larger Phase III trials for montelukast and zafirlukast have confirmed a small clinical benefit.

However, two trials, one unpublished and one published in abstract only, show montelukast and zafirlukast to be inferior in effectiveness to inhaled corticosteroids; they are also more expensive. No other trials comparing these antileukotrienes with inhaled steroids are available, so the place of antileukotrienes in the BTS guidelines cannot be assessed until more research is available.

Treatment compliance is difficult with inhaled steroid medication, thus making the oral antileukotrienes, once daily for montelukast and twice daily for zafirlukast, an attractive alternative. The effectiveness of antileukotrienes in a sub-group of patients with poor compliance with inhaled steroids (especially the very old and very young), may prove superior to inhaled steroids, but research is needed.

There is insufficient evidence to support the use of antileukotrienes in the routine prevention of asthma. For patients in whom poor compliance is suspected as a reason for inadequate response to standard treatments, a single patient cross-over (n of 1) trial comparing inhaled steroids with an antileukotriene may be appropriate, but only after intensive educational intervention by an asthma nurse has failed.

Health economic assessments were attempted, but were inconclusive, due to a lack of data. However, they do provide a guide for future research.

1. INTRODUCTION

1.1 General Introduction

Asthma is a common disease, difficult to diagnose consistently because it overlaps considerably with chronic obstructive pulmonary disease. It has a very wide range of severity occasionally leading to death, and is the cause of considerable morbidity. Better understanding of the complex pathophysiology of this condition has led to the development of drugs designed to interrupt parts of the biochemical pathways involved. The group of biochemical compounds known as leukotrienes forms part of the inflammatory response and the pharmaceutical industry has developed a number of antileukotrienes (ALTs).[1,2,3,4] Two of these, zafirlukast and montelukast, are now licensed for use in the UK and two others, pranlukast and zileuton, are licensed in other parts of the world and may subsequently be licensed for use in Europe. The major potential for this group of drugs lies in the fact that they are oral preparations, whilst current asthma preventive therapies tend to be inhaled preparations which often result in problems with compliance.

Zafirlukast has already been the subject of a 1996 report from the Wessex Institute for Health Research and Development;[5] this current document will only provide an update on this drug in response to research produced subsequent to the Wessex report. The School of Health and Related Research (ScHARR) has already prepared a detailed report on montelukast.[6] There are few published Phase III randomised controlled trials on any of these drugs.

In the UK, asthma treatment is strongly influenced by the guidelines of the British Thoracic Society (BTS) which promote a step-wise management of increasingly severe asthma.[7] Therapy consists predominantly of the use of inhalers, delivering beta$_2$-agonists, corticosteroids and cromoglycate-like drugs in various doses. The use of increasing doses of inhaled corticosteroids is the mainstay of preventive therapy; they are effective, but difficult to use.

Given the importance of the BTS guidelines, this report concentrates on the role of the ALTs in these guidelines. Unfortunately, none of the research specifically addresses this issue. This is in part because the majority of research has been carried out in the USA, where clinical opinion is more hostile to the use of inhaled steroids.

Attempts at health economic assessment are presented here, but are inconclusive. However, they do provide a guide to future research.

1.2 Incidence and Pathology

The most recent prevalence figure for patients in England suffering from asthma is 12%,[8] however, an alternative figure of 8% has also been quoted.[9]

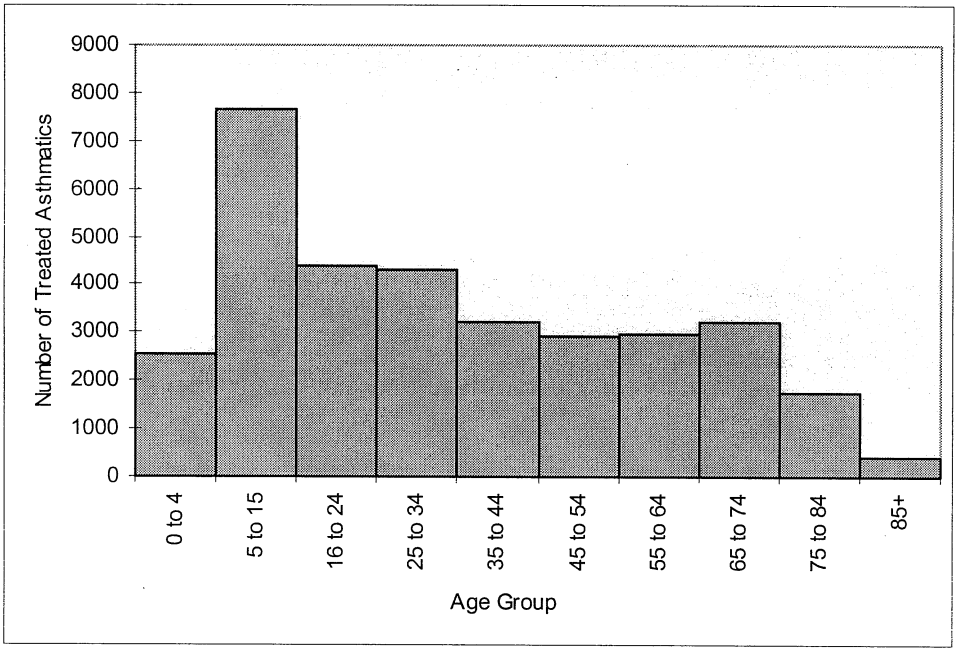
Not all people who have asthma are currently being treated. Table 1 shows the number of treated asthmatics per 1,000 population for England and Wales, broken down by age and sex.[10]

Table 1 The Prevalence of Treated Asthmatics per 1,000 Population

Age Band (years)	Male	Female
0 – 4	94.1	59.5
5 – 15	122.9	97.2
16 – 24	70.7	81.7
25 – 34	49.1	57.8
35 – 44	41.8	54.1
45 – 54	38.6	55.1
55 – 64	52.9	67.7
65 – 74	69.0	74.6
75 – 84	72.1	66.7
85 +	54.6	42.4

Assuming that these rates can be applied to a district of 500,000 people, the use of population data[11] can determine the numbers of asthmatics in each age range. These are shown in Figure 1.

Figure 1 **The Number of Treated Asthmatics in a 'Typical' District of 500,000 People**



This relates to an expected 33,500 asthma sufferers in a district of 500,000 people.

Asthma is an inflammatory disease of the lower airways caused by a variety of environmental factors such as infections, allergens, airborne chemicals and also exercise. Inflammation results in obstruction of the airways, reduced flow of gases between the air and lung alveoli and, thus, reduced exchange of oxygen and carbon dioxide between the circulating blood and lung air. As the disease worsens, blood oxygen declines and blood carbon dioxide rises.

1.3 Prognosis, Current Management and Mortality

Asthma is a disease with infinite variation in severity, going unnoticed and undiagnosed in many patients, whilst resulting in death due to asphyxia and carbon dioxide retention in a few patients. This variation is mirrored in its management, which is by a step-wise increase in medication. The BTS guidelines document, the nationally accepted best practice, and its five steps offer a treatment-based classification of severity.[7] The BTS guidelines differentiate between patients aged 0 – 4 years and those older.

Patients aged 0 to 4 years constitute 7.7% of all asthmatics.[12] However, as ALTs are not indicated for patients below the age of 4, no further work will be undertaken concerning this age band.

For patients above the age of four years, who constitute 92.3% of all asthmatics,[12] the severity of asthma has been divided into five BTS steps. The percentage of patients in each BTS step has been derived from Hoskins et al.,[13] and is shown in Table 2.

Table 2 The Estimated Proportion of People Aged 5 Years and Over with Asthma by BTS Step

	Percentage of all Asthmatics Aged 5 Years and Over
Medication below step 1	12%
BTS step 1	19%
BTS step 2	39%
BTS step 3	21%
BTS step 4	8%
BTS step 5	2%

The ALTs have been introduced as an add-on therapy after step 2 instead of progressing to the traditional step 3 medications. Thus, it has been assumed that all patients currently at step 3 would be suitable for receiving leukotrienes.

The data recorded by Hoskins et al.[13] relate to those of drugs prescribed in the 'real world'. Such prescriptions may not be in accordance with the BTS guidelines and, thus, there is a category for medication level below step 1.

The number of deaths attributed to asthma has been steadily decreasing since the end of the 1980s.[14] Data on the number of deaths in England due to asthma since 1981 are presented in Table 3 and Figure 2. Deaths occur predominantly in older people[14] and some of these may actually be attributable to chronic obstructive pulmonary disease (COPD).

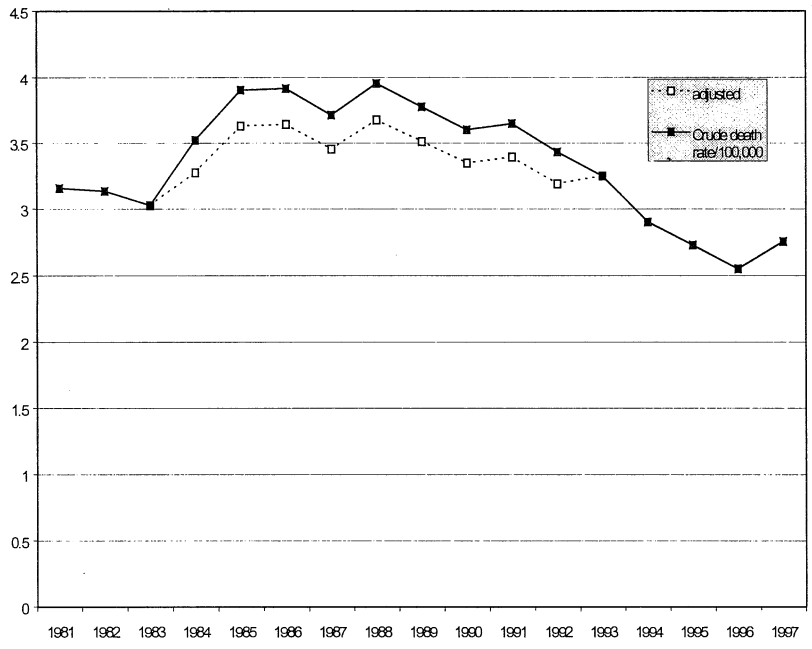
Table 3 Mortality Attributed to Asthma Between 1981 and 1997 in England

Year	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
SMR *							115	122	116	110	111	104	99	89	83	77	83
Deaths	1,477	1,467	1,418	1,654	1,839	1,850	1,760	1,879	1,801	1,722	1,754	1,655	1,577	1,414	1,335	1,253	1,358
Crude Death Rate/100,000	3.16	3.13	3.03	3.52	3.90	3.91	3.71	3.95	3.78	3.60	3.65	3.43	3.25	2.90	2.73	2.55	2.76

* The SMR (standardised mortality ratio) has been calculated based on 100 for England and Wales in 1993. (Source: Public Health Common Data Set and Office of National Statistics (ONS))

Thus, in a population of 500,000 14 deaths per year would be expected due to asthma.

Figure 2 Annual Rates of Deaths Attributed to Asthma in England Since 1981 (Deaths per 100,000 per annum) (Source: ONS)



Note: The adjustment in asthma deaths was needed because of a change in coding that affected the rates between 1984 – 1992 inclusive. It is estimated that this coding change inflated asthma deaths by approximately 7% (see Section 5.4)

1.4 Scale of Problem in a 'Typical' District

Using the prevalence rate for treated asthmatics[10] and standard population profiles[11] in a district of 500,000 people, there would be 33,501 expected asthmatics - 2,580 of these would be expected to be in the age range 0 to 4 years, and 30,921 in the age range of five years and over.

This information broken down by BTS step is given in Table 4.

Table 4 The Expected Number of People with Asthma, by Broad Age Band and Severity, in a District of 500,000 People

	Asthmatics Aged 0 - 4 Years	Asthmatics Aged 5 Years and Over
Medication below step 1	57	3,572
BTS step 1	1,204	5,783
BTS step 2	1,147	12,178
BTS step 3	172	6,463
BTS step 4	0	2,347
BTS step 5	N/A	578
Total Number	**2,580**	**30,921**

2. USE OF ANTILEUKOTRIENES: SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Direction of Evidence and its Quality

Pertinent published literature consists predominantly of reports of early-phase trials and non-systematic reviews.[15-30] Published larger Phase III trials are few: two for zafirlukast,[31,32] four for montelukast,[33,34,35,36] three for zileuton[37,38,39] and one for pranlukast.[40] All were placebo-controlled rather than comparisons with standard therapy (i.e. inhaled steroids); two[35,36] were concerned only with the effect of montelukast on exercise induced asthma and the paediatric study[33] had a population atypical of the UK where more would have been on prophylactic steroids. One of the zafirlukast papers[31] is compromised by the failure of randomisation to produce the same baseline characteristics for both arms, necessitating post-trial adjustment by multivariate analysis. A sixth paper compares zileuton with oral theophylline,[41] with zileuton being as good as, or marginally better than, theophylline.

The body of literature confirms that these four ALTs are effective as prophylactic treatments in controlling asthma but the benefits are small: up to 9% improvements in Peak Expiratory Flow Rate (PEFR) or Forced Expiratory Volume in 1 second (FEV_1); up to 12% improvements in quality of life measures such as symptom scores and activity measures. However, an abstract concerning zafirlukast[42] and data held by Merck, Sharp & Dohme on montelukast[43,44] indicate that these drugs are less effective than inhaled steroids, but with montelukast and steroids in combination being better than either alone.

Twelve cases of Churg-Strauss syndrome (allergic granulomatosis) associated with the use of zafirlukast have been reported.[15] This is a disease seen in young adults with a history of asthma. It presents as a systemic vasculitis with peripheral eosinophillia and can be acute and rapidly progressive, leading to death from heart failure; however, it responds well to steroids. As it is rare, 12 cases are a cause for concern. However, these cases have been associated with the reduction of high dose steroids, and special warnings include 'does not allow a reduction in existing steroid treatment' as well as drawing attention to Churg-Strauss syndrome.[45] No cases of Churg-Strauss syndrome have been reported through post-marketing surveillance.[15]

Table 5 Published Evidence of Clinical Effectiveness of Antileukotrienes

Lead Author	No. in Trial	Age Range (years)	Treatment Duration	Drug Tested	Comparator Drug	Primary Outcome Measures	Results
Suissa et al.[31]	146	12+	13 weeks	Zafirlukast (20mg twice daily)	Placebo	Days without asthma symptoms	Statistically significant increase in the number of days without asthma symptoms. (570% and 340% decrease from baseline for zafirlukast and placebo respectively). (p<0.05 zafirlukast vs placebo)
Fish et al.[32]	762	12 - 76	13 weeks	Zafirlukast (20mg twice daily)	Placebo	Asthma Symptoms[b] Morning FEV_1	Statistically significant decrease in asthma symptoms. Statistically significant increase in FEV_1 (6% increase and 2% decrease from baseline for zafirlukast and placebo respectively). (p<0.05 zafirlukast vs placebo)
Knorr et al.[33]	314 *chronic asthmatics*	6 - 14	8 weeks	Montelukast (one 5mg tablet per day)	Placebo	Morning FEV_1	Statistically significant increase in morning FEV_1 (8.2% and 3.6% increase from baseline for montelukast and placebo respectively) (p<0.001 montelukast vs placebo)
Reiss et al.[34]	607 *chronic asthmatics*	15+	12 weeks	Montelukast (one 10mg tablet per day)	Placebo	Morning FEV_1 Daily Asthma Symptom score [a]	Statistically significant increase in morning FEV_1 (13% and 5% increase from baseline for montelukast and placebo respectively) Statistically significant decrease after 3 weeks in daily asthma symptom score (-0.5 and –0.1 change from baseline for montelukast and placebo respectively : baseline score 2.5) (p<0.01 montelukast vs placebo)

Lead Author	No. in Trial	Age Range (years)	Treatment Duration	Drug Tested	Comparator Drug	Primary Outcome Measures	Results
Leff et al[35]	110 *exercise induced asthmatics*	15 - 45	12 weeks	Montelukast (one 10mg tablet per day)	Placebo	FEV_1 related outcomes; Maximum recovery Time to –5% recovery Area under FEV_1 curve	Statistically significant improvements in FEV_1 measures over placebo; 47.4% inhibition of FEV_1 AUC60 31.6% inhibition of maximum fall in FEV_1 26.9% inhibition of recovery time
Kemp et al[36]	27 *exercise induced asthmatics*	6 - 14	2 days	Montelukast (one 5mg tablet per day)	Placebo	FEV_1 related outcomes; Maximum recovery Time to –5% recovery Area under FEV_1 curve	Statistically significant improvements in FEV_1 measures over placebo; maximum fall in FEV_1 -18.27% vs. -26.11% for placebo (p=0.009) recovery time 17.76mins vs. 27.98 mins for placebo (p=0.079) around 59% of AUC(0-60) over placebo
Liu et al[37]	373	18-62	6 months	Zileuton (600mg doses)	Placebo	Mean change in FEV_1 Day-time asthma symptom score [b] Nocturnal asthma symptom score [b]	Statistically significant increase in FEV_1 (16% and 6% increase from baseline for zileuton and placebo respectively) ($p<0.01$ zileuton vs placebo) Statistically significant decrease in day-time asthma symptoms (36% and 20% decrease from baseline for zileuton and placebo respectively) Statistically significant decrease in nocturnal asthma symptom (35% and 6% decrease from baseline for zileuton and placebo respectively). ($p<0.05$ zileuton vs placebo)

Lead Author	No. in Trial	Age Range (years)	Treatment Duration	Drug Tested	Comparator Drug	Primary Outcome Measures	Results
Israel et al.[38]	401	18 - 60	13 weeks	Zileuton (600mg doses)	Placebo	Mean change in FEV_1 Day-time asthma symptom score [c]	Statistically significant increase in FEV_1. (13% and 5% decrease from baseline for zileuton and placebo respectively). Statistically significant decrease in daytime asthma score (-0.4 and –0.2 decrease from baseline for zileuton and placebo respectively). ($p<0.05$ zileuton vs placebo)
Barnes et al.[40]	135	18-70	6 months	Pranlukast (337.5mg doses)	Placebo	Mean change in FEV_1 Day-time asthma symptom score [d] Nocturnal asthma symptom score [d]	Statistically significant increase in FEV_1 ($p<0.05$ pranlukast vs placebo) Statistically significant decrease in day-time asthma symptoms (23% and 8% decrease from baseline for pranlukast and placebo respectively). ($p<0.05$ pranlukast vs placebo) Statistically significant decrease in nocturnal asthma symptom (28% and +8% decrease from baseline for pranlukast and placebo respectively). ($p<0.05$ pranlukast vs placebo)
Schwartz et al.[41]	313 *chronic asthmatics*	18 - 60	13 weeks	Zileuton (600mg or 400mg 4X daily)	Theophylline	Mean change in FEV_1	No statistical difference between treatments in FEV_1 measurement; 41-43% of all Zileuton patients and 46% of Theophylline patients achieved a >15% improvement in FEV_1.

PEFR - Peak Expiratory Flow Rate / FEV_1 - Forced Expiratory Volume in 1 second

[a] Using a seven point scale to rate the severity of asthma (0 indicates best, and 6 worst) [b] 0 = none, 1 = mild, 2 = moderate, 3 = severe

[c] scores range from 0 no symptoms to 3 severe symptoms [d] 0 = none, 1 = mild, 2 = moderate, 3 = severe 4 = very severe

Zafirlukast is licensed for 'the treatment of asthma', yet there are no data or guidance on how such an indication fits with the BTS guidelines. Montelukast is licensed for the treatment of 'mild to moderate persistent asthma' as 'add-on therapy in those patients who are inadequately controlled on inhaled steroids'; no trial data, constructed to support that specific indication, have been published. Indications also include 'prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction'. Whilst this is supported by evidence[35] in so much as montelukast is superior to placebo, this research does not indicate whether inhaled corticosteroids are better if prophylaxis is to be continuous (as recommended), nor does it compare montelukast with inhaled $beta_2$-agonists.

A study of the effects of montelukast on exercise-induced asthma in 6-14 year olds showed statistically significant benefits in controlling symptoms,[36] but not in a population typically found in the UK. A benefit has also been demonstrated with montelukast in adults with exercise asthma.[35] A small study of just 40 aspirin intolerant patients indicated benefit on top of any current treatment which included oral corticosteroids for some patients. However, no sub-group analysis is provided to indicate whether responses were homogenous across different baseline treatments.

Further research is needed to clarify issues on the potential use of ALTs in patients with asthma primarily due to single causes.

2.2 Treatment Compliance

Treatment compliance is an important determinant of inhaled medication and compliance is poor at about 50% (as against 79% for oral theophylline).[46] A review of this problem in the light of the development of oral ALTs[47] has suggested a potential role for these new treatments where compliance is a problem. However, the views of clinicians on the importance of compliance is divided: those attending the review seminar felt that the compliance problem is of minor importance, with other problems, especially in children, contributing far more to treatment failures.

Also, a new inhaler has been licensed recently which addresses some of the technical problems of compliance. These 'breath activated' inhalers no longer require breath co-ordinated manual triggering of the inhaler device. One such inhaler is available at the same price as generic standard inhalers. Further research is needed on the potential for improved compliance with these inhalers, especially as the compliance problem may represent a substantial niche market for the ALTs.

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

This section will be divided into two distinct parts; the first estimates the asthma burden upon society, the second attempts to bring together the costs and benefits of using ALTs.

3.1 The Cost Burden of Asthma

The costs imposed upon society by asthma can be divided into three categories.

- The direct costs of treating chronic asthma;
- The direct costs of treating an asthma attack;
- The indirect costs imposed upon society due to lost productivity due to days missed from school or work because of a patient's asthma.

An asthma attack is defined, following Neville,[48] as 'an episode of respiratory symptoms which prompts an urgent consultation with a doctor, is of sufficient severity to prevent the patient working/attending school/performing domestic duties/playing, and results in increased use of anti-asthma medication'.

The expected total number of GP/Practice Nurse (PN) consultations, out-patient attendances, Accident and Emergency department (A&E) attendances and hospitalisations due to asthma for a district of 500,000 people is shown in Table 6.

The large majority of hospitalisations will be due to asthma attacks. The GP/PN consultations will be split more evenly between general asthma management consultations and consultations prompted by an attack. The exact distribution for each resource between those used by chronic asthma management and those used due to an attack will be discussed in detail.

Table 6 **The Expected Resources Used per Annum due to Asthma for a Community of 500,000 People**

Resource	Number of People Aged 5 Years and Over with Asthma
GP / PN consultations[49]	38,075
Out-patient attendances[13]	3,980
A&E dept. attendances[13]	748
Hospitalisations[50]	680

3.1.1 The Direct Costs Incurred by Treating Chronic Asthma

The costs incurred in treating chronic asthma can be divided into four categories of expenditure:

- prescribed drugs;
- elective hospitalisations;
- elective out-patient attendances;
- GP/PN consultations.

3.1.1.1 Drugs Prescribed for Chronic Asthma

The largest cost in treating chronic asthma is the prescribed drugs taken by asthmatics. The use of Prescribing Analysis and Costs (PACT) data to determine the quantity of drugs prescribed for asthma would produce inaccurate results as some of the same drugs are prescribed for other respiratory diseases such as COPD. The division of the drug costs by BTS step could also not be determined by the use of PACT data.

To calculate the number and costs of drugs prescribed for asthma, it has been assumed that the patients are prescribed drugs consistent with their position within BTS guidelines.

The assumed drug regimens for patients on each BTS step are given in Table 7 for patients aged five years and over.

Table 7 **The Assumed Drug Regimens Per BTS Step for Patients Aged 5 Years and Over**

BTS step	Assumed Drug Use
Below Step 1	Salbutamol 0.5 puffs a day.
Step 1	Salbutamol 1 puff a day.
Step 2	Beclomethasone 200ug twice daily + Salbutamol 4 puffs a day.
Step 3	Beclomethasone 400ug four times daily + Salbutamol 4 puffs a day.
Step 4	Step 3 treatment + Salmeterol 50ug twice daily
Step 5	Step 4 treatment + 5mg Prednisolone once daily

The yearly costs of these drug regimens have been calculated with the use of the electronic version of the British National Formulary.[51] The costs per step are shown in Table 8 for patients aged five years and over. The full calculations for each age group are given in Appendix A.

Table 8 **The Expected Drug Costs Per BTS Step for Asthmatics Aged 5 Years and Over in a District of 500,000 People per Annum**

BTS Step	Drug Cost per Year per Patient	No. of People in the Step	Total Drug Costs
Below Step 1	£1.57	3,572	£5,608
Step 1	£3.14	5,783	£18,159
Step 2	£84.19	12,178	£1,025,265
Step 3	£299.06	6,463	£1,932,825
Step 4	£647.27	2,347	£1,519,142
Step 5	£668.31	578	£386,283
All Steps	N/A	30,921	£4,887,282

3.1.1.2 Elective Hospital Admissions Due to Chronic Asthma

Table 6 showed that there would be an expected 680 admissions to hospital of patients aged five years and over, due to asthma. The large majority of these will be due to asthma attacks, although some will be elective admissions. An analysis of the Trent Patient Information System database showed that only 3% of admissions due to asthma for patients aged five years and over were elective. Applying this percentage to the total hospital admissions there would be around 20 elective admissions per annum for patients aged five years and over.

An attack resulting in hospitalisation has been costed at £369.26 for an asthmatic child aged 0 – 4 years and £857.69 for an asthmatic child aged five years and over. The full costing details can be found in Appendix B.

The total hospitalisation costs are shown in Table 9.

Table 9 The Expected Elective Hospitalisation Costs per Annum for Asthmatic Patients in a District of 500,000 People

Asthmatic Age Band	Expected No. of Elective Hospitalisations	Cost per Hospitalisation	Total Cost
5 years and over	20.4	£857.69	£17,497.88

3.1.1.3 The Number of Elective Out-Patient Attendances

It has been assumed that the percentage of elective out-patient attendances is equal to the percentage of elective hospitalisations. As this is only 3% for patients aged five years and over, the costs of elective out-patient attendances will be assumed to be zero and all out-patient attendance costs apportioned to asthma attacks.

The cost of an out-patient follow-up has been estimated at £50.00, the cost of an A&E attendance has been estimated at £52.34.[53]

3.1.1.4 The Number of GP Consultations Due to Treating Chronic Asthma

In order to calculate the number of GP consultations due to treating chronic asthma, it has been assumed that the average asthma attack would require two GP visits, one at the onset of the attack and one as a patient follow-up. This assumption was based on the findings of a Merck Sharp Dohme sponsored study of GP support in managing asthmatic patients (January 1999).[52]

It will be shown that there are an estimated 6,363 asthma attacks in patients aged five years and over per annum in a community of 500,000 people. Given the assumption of two GP consultations as a result of an asthma attack, there would be an estimated 12,726 GP consultations for patients aged five years and over. Subtracting these figures from the total GP consultations given in Table 6 gives an estimate of 25,349 consultations for chronic asthma in patients aged five years and over.

The expected cost of GP consultations for chronic asthma is shown in Table 10. The cost of a GP/Practice Nurse (PN) consultation has been estimated as £15.00.[53]

Table 10 The Expected Cost of GP Consultations for Chronic Asthma per Annum in a District of 500,000 People

Asthmatic Age Band	Expected No. of GP/PN Consultations for Chronic Asthma	Cost per GP/PN Consultation for Chronic Asthma	Total Cost
5 years and over	25,349	£15.00	£380,235

3.1.1.5 Summarising the Direct Costs of Treating Chronic Asthma

The estimated costs of treating chronic asthma are shown in Table 11.

Table 11 **The Expected Total Costs for Treating Chronic Asthma per Annum in a District of 500,000 People**

Expenditure Category	5 Years and Over	% of Total
Prescribed Drugs	£4,887,282	92.5%
GP Consultations for Chronic Asthma	£380,235	7.2%
Elective Hospitalisations	£17,498	0.3%
Total	**£5,285,015**	**100%**

It can be seen that the largest component of expenditure on chronic asthma is prescribed drugs.

3.1.2 The Direct Costs of Treating Asthma Attacks

The direct costs for treating an asthma attack can be divided into the following categories of expenditure:

- GP/PN consultations;
- Hospital admissions;
- Out-patient attendances;
- A&E attendances.

The rate of asthma attacks in the community is 1.43 attacks per 100 people.[48] Thus, in a district of 500,000 people, there would be an expected number of 7,150 attacks. It is expected that 11%[13] (787) of these attacks will be in patients aged 0-4 years, with 6,363 attacks for patients aged five years and over.

3.1.2.1 The Expected Number of GP/PN Consultations for Treating Asthma Attacks

It has been assumed that each asthma attack will require two GP/PN consultations. As such, there will be an expected 12,726 consultations for patients aged five and over. The costs of

these consultations are given in Table 12. The cost of a GP/PN consultation has been set as £15.00.[53]

Table 12 The Expected Cost of GP Consultations Per Annum due to Asthma Attacks in a District of 500,000 People

Asthmatic Age Band	Expected No. of GP/PN Consultations Due to Asthma Attacks	Cost per GP/PN Consultation Due to Asthma Attacks	Total Cost
5 years and over	12,726	£15.00	£190,890

3.1.2.2 The Expected Number of Hospital Admissions for Treating Asthma Attacks

The number of hospitalisations for asthma in England was 94,673 in 1994/95.[50] This was for a population of 48.7m.[11] Assuming that there is little difference in prevalence throughout England it would be expected that there would be 972 hospital admissions in a community of 500,000 people, of which a small proportion will be elective.

The distribution of the hospital admissions was divided into 30% for patients aged 0-4 years and 70% for patients aged five years and older.[50] This division will be used in the analysis; however, Duffy et al. have given an alternative of 21% and 79% respectively.[54] These data suggest 680 hospital admissions in those patients five years of age and over. From this figure is also subtracted the number of elective hospitalisations for chronic asthma, previously calculated at just over 20 per annum. The expected number of hospitalisations, and the cost for the age band five years and over are given in Table 13. The cost for a hospital admission has been calculated in Appendix B.

Table 13 The Expected Hospitalisation Costs per Annum due to an Asthma Attack in a District of 500,000 People

Asthmatic Age Band	Expected Number of Hospitalisations Due to an Asthma Attack	Cost Per Hospitalisation	Total Cost
5 years and over	660	£857.69	£566,075

3.1.2.3 The Number of Out-patient Attendances and A&E Attendance due to Asthma Attacks

It has been assumed that all out-patient attendances and A&E attendances are the results of asthma attacks (this is a 'conservative' assumption as it gives more favourable cost-effectiveness ratios for interventions which decrease asthma attacks). As such, referring to Table 6, there would be an expected 3,980 out-patient attendances and 748 A&E attendances per year for patients aged five years and over.

The cost of an out-patient follow-up has been estimated at £60.00; the cost of an A&E attendance has been estimated at £98.00.[53]

The annual estimated expenditure for elective out-patient attendances and A&E attendances is shown in Tables 14 and 15 respectively.

Table 14 The Expected Out-patient Attendance Costs per Annum due to Asthma Attacks in a District of 500,000 People

Asthmatic Age Band	Expected No. of Elective Out-patient Attendances	Cost Per Out-patient Follow-up	Total Cost
5 years and over	3,980	£60.00	£238,800

Table 15 **The Expected A&E Attendance Costs per Annum for Patients with Asthma in a District of 500,000 People**

Asthmatic Age Band	Expected No. of A&E Attendances	Cost Per A&E Attendance	Total Cost
5 years and over	748	£98.00	£73,304

3.1.2.4 Summarising the Direct Costs of Treating Asthma Attacks

The estimated costs of treating asthma attacks are shown in Table 16.

Table 16 **The Expected Total Direct Costs per Annum for Treating Asthma Attacks in a District of 500,000 People**

Expenditure Category	5 Years and Over	% of Total
Hospitalisations due to asthma attacks	£566,075	53.0%
Out-patient attendances after asthma attacks	£238,800	22.3%
GP consultations for asthma attacks	£190890	17.9%
A&E attendances for asthma attacks	£73,304	6.9%
Total	**£1,069,069**	**100%**

It can be seen that the majority of expenditure in treating asthma attacks is on hospital admissions.

3.1.3 The Indirect Costs Attributed to Asthma

The most recent published estimates of the indirect cost burden caused by asthma are given in Table 17. These costs, particularly the cost of lost productivity, are dated and it can be assumed that the costs are now higher.

Table 17 The Estimated Annual Level of Indirect Costs per Annum

Indirect Cost Category	Total Cost for Britain	Total Cost in a District of 500,000 people
Lost Productivity (1990)[55]	£342m	£3.03m

Sickness and Invalidity benefits of £179m in 1995[56] have not been included as these are transfer payments.

The population of Britain was 56.4m in 1991.[57] If it is assumed that this population has been constant and that the distribution of asthma was spread evenly, then the expected indirect costs incurred annually for a population of 500,000 would be at least £3 million.

3.1.4 The Total Direct and Indirect Costs Attributed to Asthma

The total direct and indirect costs attributed to asthma are given in Table 18.

Table 18 Summarising the Annual Burden of Asthma in Patients Aged 5 Years and Over within a District of 500,000 People

Cost Category	Total Cost
Treating Chronic Asthma	£5.29m
Treating Asthma Attacks	£1.07m
Indirect Costs Incurred	£3.42m
All Categories	**£9.39m**

3.2 The Economic Impacts of Prescribing a Patient Antileukotrienes as an Alternative to Increasing the Level of Steroids

In considering the potential relative treatment costs for inadequately controlled asthmatic patients moving to step 3 of the BTS guidelines, the authors have compared the use of additive ALTs with low dose inhaled corticosteroids against a strategy of increasing the dosage of inhaled corticosteroids.

It is estimated that a yearly course of ALTs will cost £335.12 (Appendix A). The potential increase in inhaled steroids is assumed to be from 200ug twice daily to 400ug four times a day (representing a significant increase as suggested by existing BTS guidelines). This has been costed as beclomethasone, which is the most commonly prescribed inhaled steroid. Appendix A shows that this is an expected increase in annual cost of £214.87 (the difference in increasing from £71.63 to £286.50). Hence, the use of additive ALT would be expected to increase annual patient drug costs by around £120 per person (the difference between the £214.87 and £335.12 increases for corticosteroids and ALTs respectively). This assumes no tapering of inhaled corticosteroid whilst on ALT and is limited to asthma drugs only.

In a district of 500,000 population there are expected to be 6,463 patients aged five years and over (refer to Table 4) who are at step 3. Based on these levels of drug cost increase then the cost to treat all these patients with ALTs would be an additional £777,176.

The economic rationale for prescribing ALTs will be to reduce the level of asthma attacks, either through better medication or from increased compliance. The current direct cost burden from asthma attacks for patients for whom ALTs are applicable has been calculated.

ALTs are targeted at those adult patients progressing from step 2 to step 3. In order that the costs used in these groups are shown, the attacks in patients aged five years and over have been broken down into BTS step profile.[48] This is shown in Table 19.

Table 19 **The Percentage of Attacks by BTS Step in Patients Aged 5 Years and Over**

BTS Step	% of Attacks	Expected No. of Attacks per Annum in a Community of 500,000 People
Step 0*	23%	1,463
Step 1	24%	1,527
Step 2	23%	1,463
Step 3	20%	1,273
Step 4	7%	445
Step 5	3%	191
All Steps	100%	6,363

* Those patients who were not previously upon a BTS step.

Assuming that ALTs would be an add-on therapy to step 2 treatment, as an alternative to traditional step 3 treatment, then there would be an estimated 1,273 attacks in patients who could have been prescribed ALTs. Assuming 2 GP/PN consultations per attack at a cost of £15.00 per consultation, the cost burden for step 3 asthma attacks would be £19,095.

The hospitalisations of patients aged five years and over have been broken down into the BTS steps from data from Duffy et al.[54] However, these data were applicable only for patients aged 16 years and over and slight inaccuracies may result when applied to patients aged five years and over. The estimated number of hospitalisations per BTS step is given in Table 20.

Table 20 **The Expected Annual Number of Hospitalisations due to Asthma Attacks per BTS Step for Patients Aged 5 Years and Over in a District of 500,000 People**

BTS Step	% of Hospitalisations Due to an Asthma Attack	Expected No. of Hospitalisations per Annum in a District of 500,000 People
Step 0*	3%	20
Step 1	9%	59
Step 2	16%	106
Step 3	20%	132
Steps 4 and 5	52%	343

* Those patients who were not previously upon a BTS Step.

There were 132 hospitalisations due to an asthma attack expected for patients at step 3. This is the maximum possible reduction in the number of asthma attacks which could be theoretically prevented were the patients prescribed leukotrienes as a step 3 alternative. This represented 20% of all asthma attack hospitalisations for patients aged five years and over. Applying this percentage to the total costs for hospitalisation, out-patient attendances and A&E attendance costs caused by attacks for patients aged five years and over, the maximum cost reductions were £113,215, £47,760 and £14,661 respectively.

The total savings which would be made, were **all** step 3 asthma attacks to be prevented, are summarised in Table 21. It is to be noted, however, that they are almost certainly based on an overestimate of the asthma attack reduction.

Table 21 The Potential Cost Savings were there to be no Step 3 Asthma Attacks in Patients Aged 5 Years and Over in a District of 500,000 People

Expenditure Category	5 Years and Over	% of Total
Hospitalisations due to asthma attacks	£113,215	58.2%
Out-patient attendances after asthma attacks	£47,720	24.5%
GP consultations for asthma attacks	£19,095	9.8%
A&E attendances for asthma attacks	£14,661	7.5%
Total	£194,691	100%

Thus, it is estimated that, were all step 3 asthma attacks prevented, the direct cost savings would be £194,691.

It is assumed that lost productivity relates purely to the asthmatic age group above four years. If it were assumed further that such costs were the results of asthma attacks, it would not appear unreasonable to proportion the costs in relation to the percentage of attacks at each BTS step. As 20% of all asthma attacks in patients aged five years and over, occurred when the patient was at step 3,[48] an estimate of the indirect costs for those people who could have been prescribed ALTs is £3,031,915 x 0.2 = £606,383.

The expected additional cost of prescribing ALTs is known (£777,176), as is the potential saving in both direct costs (£194,691) and indirect costs (£606,383), were there to be no step 3 asthma attacks.

Analysing direct costs only, it can be seen clearly that prescribing ALTs to all patients at step 3 cannot produce a monetary saving as the prescribing costs are four-times that of the saving.

Analysing both direct and indirect costs, it is noted that the number of attacks within step 3 would need to be reduced by 97% in order for ALTs to be cost neutral. At this level of

reduction the annual direct and indirect costs averted (97% x (£194,691 + £606,383)) are equal to the additional annual prescribing expenditure (£777,176).

An indication of whether such a reduction is likely, can be determined by assuming that the use of ALTs reduces the attack rate in step 3 to the attack rate in step 2.

There are an estimated 12,178 people in step 2, and 6,463 people in step 3 (refer to Table 4), who suffer 1,463 and 1,273 attacks respectively (refer to Table 19). These produce attack rates of 12.0% and 19.7% for steps 2 and 3 respectively. This assumption would reduce the number of attacks by 39%, which is substantially below the previously calculated 97% reduction threshold level for cost neutrality.

However, it is likely that these figures underestimate the cost increase associated with ALTs. The analysis has assumed an increase in medication from 400ug beclamethasone to 1600ug beclamethasone, when a patient changes from step 2 to step 3. For these patients, it is likely that they would be on a higher dose of corticosteroid at step 2 than the 400ug per day. If, for example, 800ug/day beclamethasone was the initial step 2 dosage level before increasing to the same level of higher dosage, the increase in the additional drug expenditure when prescribing ALTs would be £191.87 per patient (increase in costs of £335.12 compared to £143.25). This would total £1,240,056 for all step 3 patients. This increase in initial corticosteroid dosage results in the additional prescribing expenditure (£1,240,055) being greater than the level of direct and indirect cost which could be avoided (£194,691 + £606,383).

Finally, if the addition of ALTs was compared to the alternative BTS step 3 strategy of introducing a twice daily inhaled dose of salmeterol then this increase in annual patient drug costs would be around £10-15 (the difference between the £348.21 and £335.12 additional costs of salmeterol and ALT respectively).

However at present, there is no published information on the effectiveness of inhaled steroids and ALTs compared with increasing the dosage level of inhaled steroids (or indeed the addition of long-acting beta 2 drugs). Until these data become available, no conclusion can be made on the cost-effectiveness of ALTs.

3.3 Potential Quality of Life Improvements

The preceding economic analyses have been calculated upon the assumption that ALTs would be given to all patients over the age of five years as an alternative to step 3 options. These analyses have been confined to basic cost comparisons only, as there are no published data comparing the use of low-level doses of inhaled steroids and ALTs with high-level doses of inhaled steroids.

However, there are clearly a number of patient outcomes (e.g. nocturnal awakenings, symptom-free days and asthma exacerbations) which, whilst not being directly linked to usage of health care services, can impact very much on a patient's general quality of life and overall life function.

The subsequent analyses estimate the quality of life improvement which would be necessary in order that the cost per Quality Adjusted Life Year (QALY) was equal to £2,000 (given our previous calculation of marginal drug cost over higher corticosteroid dosage treatments). This £2,000 per QALY level has been chosen for illustrative purposes only, as a level that may be proved acceptable to a typical health authority commissioner of asthma services.

The analysis does not represent a formal cost utility analysis as, again, there are no direct comparative data upon which to make such judgements. However, it provides an indication of the degree of impact in terms of life quality which ALTs would have to have if they were to be considered effective using cost utility analysis.

If it were assumed that the increase in beclamethasone between steps 2 and 3 was from 400ug to 1600ug, the additional annual cost of not increasing the dose but adding an ALT is estimated at £120.25 per person. In order for the cost per QALY to equal £2,000, the improvement in the quality of life by adding ALTs rather than increasing the dose of steroids would have to be approximately 0.06.

If it were assumed that the increase in beclamethasone between steps 2 and 3 was from 800ug to 1600ug, the additional annual cost of not increasing the dose, but adding an ALT, is estimated at £191.87 per person. In order for the cost per QALY to equal £2,000, the improvement in the quality of life by adding an ALT rather than increasing the dose of steroids would have to be approximately 0.1.

Formal analysis of the quality of life impacts of ALTs are required, along with an estimate of a patient's utility for improvements in asthma symptoms and exacerbations.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

These are as follows:

Option 1 To discourage the use of ALTs until further research is available, or the BTS has issued guidance.

Option 2 To support ALT use only through secondary care asthma centres, ensuring systematic and co-ordinated data collection, preferably in appropriately designed trials.

Option 3 To commission regional interim guidelines for use in primary and secondary care, possibly targeting patients with problems of inhaled steroid compliance.

5. DISCUSSION AND CONCLUSION

5.1 Antileukotrienes versus Inhaled Corticosteroids and Other Current Treatments

ALTs are effective in the preventive management of chronic asthma: they are better than placebo, but, on the basis of only limited data, less effective than inhaled corticosteroids. Whilst the efficacy of ALTs is inferior to inhaled corticosteroids, compliance with inhaled treatments is poor and in a proportion of patients for whom compliance is particularly problematic, ALTs may be more effective than inhaled steroids. However, even then their cost-effectiveness is not known.

ALTs have a relatively rapid onset (within hours) and there is no evidence of progressive change with prolonged use (cf. steroids); it may be appropriate, therefore, to consider them as an alternative to long-acting beta-agonists (e.g. salmeterol).

Trials involving direct comparison with inhaled corticosteroids and long-acting beta-agonists are urgently needed, with UK trials concentrating on studying the place of ALTs in the BTS guidelines, especially step 3.

5.2 Treatment Compliance and Antileukotrienes

Montelukast, once daily, and zafirlukast, twice daily, offer considerable potential in dealing with the problem of compliance with inhaled corticosteroids. As zileuton and pranlukast are both four times daily doses, they are likely to be less beneficial than the other two ALTs. Targeting ALTs at this poor compliance sub-group could go some way to achieving overall effectiveness of chronic asthma prevention closer to theoretical treatment efficacy. Further research is required, which will need to include the use of the new breath activated inhaler devices.

5.3 Antileukotrienes in Sub-Groups

ALTs have been studied in the treatment of sub-groups of patients with a single underlying cause of their asthma predominating e.g. montelukast for exercise induced asthma and zileuton for aspirin induced asthma. In neither case has the trial included direct comparison with inhaled corticosteroids.

Leukotrienes are released in the respiratory tract during acute viral infections[58] and such infections are associated with significant morbidity and admissions to hospitals due to acute asthma attacks. A short course of ALTs at the time of such respiratory infections may be highly beneficial and should be the subject of a clinical trial. A cheap, but accurate, near-patient test for urinary leukotrienes might also assist in targeting ALTs at a sub-group of patients in whom leukotrienes are a major mediator in their asthma.

5.4 Trends in Asthma Deaths

Interpretation of trends in asthma mortality is difficult, both because of the overlap with COPD, the degree of overlap changing over time, and the problem of changes in ONS coding affecting records between 1984 and 1992 (inclusive), a period when asthma deaths peaked. Deaths due to asthma recorded by both methods are reported in the 1984 Mortality Statistics[59] and an estimate of 'excess' deaths was made for 1990 to 1992,[60] these would suggest an over-reporting during the nine years of about 7%.

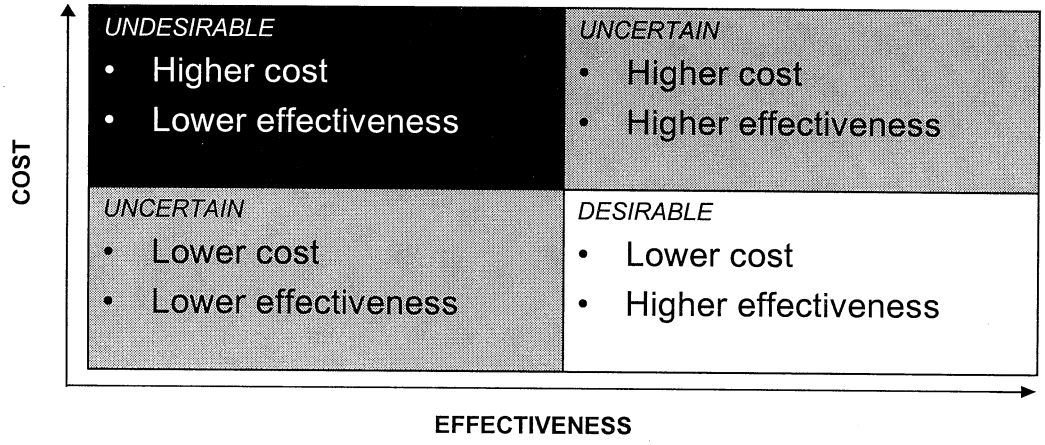
5.5 The Impact of British Thoracic Society Guidelines

BTS guidelines were first published in 1990; the downward trend in deaths may have started in 1988 or 1991, but has been consistently downwards from 1991 until the recent rise in 1997. It might be reasonable to conclude that the BTS guidelines have resulted in at least some of this improvement and, therefore, that it would be unwise to deviate from the guidelines until better data are available. Even then, it is going to be very difficult to identify any effects of ALTs, when introduced, on death rates because of the relatively small number of deaths and the problems of linking individual deaths with treatment regimens.

5.6 Health Economic Analysis

The analysis presented here has been unable to answer important questions, because of lack of data. Nonetheless, some issues are clear when they are considered in terms of a marginal cost-effectiveness matrix as shown in Figure 3. This points the way forward for future research.

Figure 3 The Marginal Cost-effectiveness Matrix



ALTs in the routine prophylaxis of chronic asthma fit into the top left-hand corner and, thus, are shown to be an undesirable new intervention. Targeted ALTs are likely to fall in the upper right quadrant and further research would be required to clarify their cost-effectiveness profile.

5.7 Side-effects

Whilst ALTs are relatively free of side-effects and well tolerated, their long-term risks are unknown; 30 years after the introduction of inhaled steroids the debate on their risks, especially in children, still continues. ALTs suppress an apparently important host defence function and could have long-term adverse consequences.

5.8 Other Health Technology Assessments and a Recent Clinical Review

The conclusions of two other independent Heath Technology Assessments (HTAs) and a clinical review from the Canadian Coordinating Office for Health Technology Assessment,[61] The Drug and Therapeutics Bulletin[62] and the BMJ[63] are included at Appendix C for ease of access, and reach similar conclusions.

5.9 Suggestions for Further Research

- Direct comparison of ALTs against alternative treatments for various steps in the BTS guidelines, e.g. increased dose of steroids or long-acting $beta_2$-agonists.

- Appropriately conducted trials directed at patients with poor compliance, concentrating in particular at health economic issues.
- The use of ALTs as treatment for, or prophylaxis of, asthma induced by viral respiratory infections, compared with current alternatives.
- Comparisons between all treatment options for the management of exercise induced asthma, including marginal cost-effectiveness of combined treatments, be it continuous or as needed prophylaxis.
- Comparisons between treatments for aspirin sensitive asthmatics.
- The establishment, at an early stage, of longitudinal studies of the long-term effects of ALTs, when they are prescribed, especially in children.
- A study of the effectiveness and cost-effectiveness of ALTs in patients who respond well to ALTs (by subsequent randomisation to ALTs or standard treatment).

5.10 Addenda

Publication of this report has been delayed, during which time more recent research will have come close to publication. That research may answer some of the questions in 5.9 above, and necessitate revisiting the recommendations made here. Nonetheless, that research, when published, must be subject to the same degree of critical appraisal as here, before recommendations can be changed.

The recent Drug and Therapeutics Bulletin review of inhaled corticosteroids in childhood asthma[64] draws attention to the benefits, but also potential side-effects of inhaled steroids and the morbidity associated with poor control of asthma in childhood. A long-term study of the potential benefits and problems of ALTs, as compared to inhaled steroids, in childhood asthma is needed. The review also concludes that inhaled steroids are not as effective in viral induced episodic wheezing, confirming the need for trials of alternative treatments, including ALTs.

APPENDIX A Costing Selected Drug Regimens

Patients Aged Five Years and Over

Salbutamol 0.5 puffs a day:

Costed as 50% upon Ventolin (A&H) (cost for a 200 dose unit £2.30) and 50% upon non-proprietary (200 dose unit £1.14)

Number of units used per year = (365.25 x 0.5) / 200 = 0913125

Assumed unit price = 0.5 x £2.30 + 0.5 x £1.14 = £1.72

Cost per year = 0.913125 x £1.72 = £1.57

Salbutamol 1 puff a day:

Costed as 50% upon Ventolin (A&H) (cost for a 200 dose unit £2.30) and 50% upon non-proprietary (200 dose unit £1.14)

Number of units used per year = (365.25 x 1) / 200 = 1.82625

Assumed unit price = 0.5 x £2.30 + 0.5 x £1.14 = £1.72

Cost per year = 1.82625 x £1.72 = £3.14

Beclomethasone 200ug twice daily

Costed as Becotide (A&H) 200ug (200 dose unit £19.61)

Number of units used per year = (365.25 x 2) / 200 = 3.6525

Cost per year = 3.6525 x £19.61 = £71.63

Beclomethasone 200ug four times daily

Costed as Becotide (A&H) 200ug (200 dose unit £19.61)

Number of units used per year = (365.25 x 4) / 200 = 7.305

Cost per year = 7.305 x £19.61 = £143.25

Beclomethasone 400ug four times daily

Costed as Becotide (A&H) 200ug (200 dose unit £19.61)

Number of units used per year = (365.25 x 8) / 200 = 14.61

Cost per year = 14.61 x £19.61 = £286.50

Salmeterol 50ug twice daily

Costed as Serevent (A&H) 25ug (120 dose unit = £28.60)

Number of units used per year = (365.25 x 4) / 120 = 12.175

Cost per year = 12.175 x £28.60 = £348.21

5mg Prednisolone once per day

Costed as Prednesol (Glaxo Wellcome) 5mg (100 tab pack £5.76)

Number of packs per year = (365.25 x 1)/100 = 3.6525

Cost per year = 3.6525 x £5.76 = £21.04

10mg of Antileukotrienes once per day

Costed as Singulair (Merck Sharp Dohme) 10mg (28 tablet box £25.69)

Number of boxes per year = (365.25 x 1)/28 = 13.045

Cost per year = 13.045 x £25.69 = £335.12

APPENDIX B The Costs of a Hospital Admission due to Asthma

The rescue medications assumed to be given to a patient having an asthma attack that required hospitalisation are given in Table B1.

Table B1 The Assumed Drugs Given to Stabilise an Asthma Attack

Drug	Dosage	Costed as
Prednisolone	30mg per day for 7 days	Prednesol (Glaxo)
Nebulised Salbutamol	5ml 6 times a day for 3.3 days	Ventolin Nebules (A&H)
Nebulised ipratopium bomide	250ug four times a day for 1 day	Atrovent (Boehringer Ingelheim)
Amoxycillin (only for 10% of patients)	500 mg thrice daily for 7 days	Non-proprietary

The costs of these drugs are shown in Table B2.

Table B2 The Cost of the Drugs Given to Stabilise an Asthma Attack

Drug	Cost per unit	Cost per attack
Prednesol (Glaxo)	100 5mg tablets cost £5.76	£2.41
Ventolin Nebules (A&H)	2.5 ml cost 19p	£7.52
Atrovent (Boehringer Ingelheim)	20 250ug doses cost £6.75	£1.35
Amoxycillin (only for 10% of patients)	20 500mg tablets cost £1.05	£0.11
Total Cost	N/A	£11.39

The average lengths of stay for a hospital admission due to asthma and the average costs per day, for the age range 5 years and over are given in Table B3. Duffy et al.[54] have published a not dissimilar figure of 4.2 days for all ages.

Table B3 Average Lengths of Stay and Costs per Day following Hospitalisation due to Asthma

Age Band	Average Length of Stay	Cost Per Day	Cost Per Stay
5 years and over	4.34 [a]	£195 [b]	£846.30

[a] Analysis taken from the Trent PIS database

[b] Standard costs taken from Netton and Dennet 1996.[53]

The total costs of a hospital admission for asthma are given in Table B4.

Table B4 The Total Costs for a Hospitalisation due to Asthma

Age Band	Cost of Rescue Medication	Cost Per Stay	Total Cost
5 years and over	£11.39	£846.30	£857.69

APPENDIX C Conclusions from Independent Health Technology Assessments

CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT (CCOHTA): ISSUES IN EMERGING HEALTH TECHNOLOGIES: Issue 3; April, 1998[61]

Antileukotrienes: an emerging generation of drug therapies for asthma.

SUMMARY:

Based on current evidence, ALTs have a role in maintenance therapy in some mild to moderate asthmatics. However, long-term and comparative studies (i.e. versus inhaled corticosteroids (ICSs)) have yet to be published, and the role of ALTs as first line therapy or in severe asthma is unknown.

The benefits of these agents in terms of their impact on symptoms and pulmonary function are consistent; however, their impact on the use of inhaled corticosteroids or beta-agonists is still not known.

Adverse events have been reported. Long-term monitoring of patients (an additional cost), will be required to determine the safety of these drugs.

Oral formulations may contribute to improve compliance and drug delivery (and, thus, efficacy); but only limited (short-term) information is available for children, where this route would be particularly advantageous.

Some of the costs (see Table 2) and the cost-effectiveness of these agents have yet to be determined.

DRUG AND THERAPEUTICS BULLETIN 1998 VOL.36, SEPTEMBER 1998[62]

Montelukast and Zafirlukast in Asthma.

CONCLUSION:

Montelukast and zafirlukast belong to a new class of drugs for asthma, the leukotriene receptor antagonists. Both drugs improve symptoms and surrogate markers of asthma's severity, but the improvements are small. None of the clinical trials published in full compare montelukast or zafirlukast with conventional treatments for asthma. Moreover, there is little or no evidence for montelukast's promoted use as an add-on therapy in patients whose asthma is not adequately controlled by $beta_2$-agonists and inhaled corticosteroids. Until studies have been published which define the place of these drugs in relation to standard approaches, it is difficult to assess their usefulness in the treatment of asthma, either alone or in conjunction with conventional drugs. In the absence of such trials, an alternative is to carry out single-patient randomised trials of leukotriene antagonist therapy, which would require the provision of appropriate placebos.

BMJ 1999;318:380-384 (6 FEBRUARY)[63]

Modern Drug Treatment of Chronic Asthma

Brian J Lipworth, Professor of Allergy and Respiratory Medicine.

CONCLUSION:

Further long-term studies are required to evaluate the position of leukotriene antagonists as first line preventer treatment instead of low dose inhaled corticosteroid drugs in patients with mild to moderate asthma.

APPENDIX D Suggestions for Further Research

1. A double-blind cross-over study of the effectiveness of montelukast in ameliorating acute viral wheezing episodes in young children.

2. The use of ALTs in children (and possibly adults) with troublesome exercise-induced asthma but, otherwise, well controlled on preventative therapy.

3. Which is the most appropriate step 3 change: increased inhaled steroids or the addition of long-acting beta-agonists or the addition of an ALT?

REFERENCES

1. O'Byrne PM. Leukotrienes in the pathogenesis of asthma. *Chest* 1997; 111(2 Suppl): 27S-34S.

2. Larsen JS, Jackson SK. Antileukotriene therapy for asthma. *Am J Health Syst Pharm.* 1996; 53: 2821-2830.

3. Horwitz RJ, McGill KA, Busse WW. The role of leukotriene modifiers in the treatment of asthma. *Am J Respir Crit Care Med* 1998; 157:1363-1371.

4. Tan RA. The role of antileukotrienes in asthma management. *Curr Opin Pulm Med* 1998; 4: 25-30.

5. Wessex Institute for Health Research and Development Development and Evaluation Committee; Zafirlukast (Accolate ™) in Asthma. 1996; Report 64.

6. Beard S, Ward S, Fishwick D. The Role of Montelukast in the Management of Inadequately Controlled Asthma *(Unpublished).*

7. British Thoracic Society. The British Guidelines on Asthma Management, *Thorax* 1997; 52: Suppl 1.

8. The Department of Health. Health Survey for England 1996. London, The Stationery Office.

9. European Community Respiratory Health Survey Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey. *Eur Respir J* 1996; 9: 687-695.

10. Key Health Statistics from General Practice 1996. Series MB6 no 1 ONS.

11. Key Population and Vital Statistics 1994 VS no 21 PP1 no 17 ONS.

12. Derived from Key Health Statistics from General Practice 1996. Series MB6 no 1 ONS and Key Population and Vital Statistics 1994 VS no 21 PP1 no 17 ONS.

13. Hoskins G, Smith B, Neville R, et al. The Tayside Asthma Management Initiative. *Health Bull* 1998; 56: 586-591.

14. Mortality Statistics ONS, Series DH2 nos 21-23.

15. Calhoun WJ. Summary of clinical trials with zafirlukast, *Am J Respir Crit Care Med* 1998; 157 (6pt2): S238-245.

16. Spector SL. Management of asthma with zafirlukast. Clinical experience and tolerability profile. *Drugs* 1996; 52 (Suppl 6): 36-46.

17. Adkins JC, Brogden RN. Zafirlukast. A review of its pharmacology and therapeutic potential in the management of asthma. *Drugs* 1998; 551:121-144.

18. Hendeles L, Marshik PL. Zafirlukast for chronic asthma: convenient and generally safe, but is it effective? *Ann Pharmacother* 1997; 31:1084-1086.

19. Kelloway JS. Zafirlukast the first leukotriene-receptor antagonist approved for the treatment of asthma. *Ann Pharmacother* 1997; 31:1012-1021.

20. Chung KF, Barnes PJ. Zafirlukast (Accolate™). *Drugs of Today* 1998;34: 375-88.

21. Reiss TF, Sorkness CA, Stricker W, et al. Effects of montelukast (MK-0476) a potent cysteinal leukotriene receptor antagonist, on bronchodilation in asthmatic subjects treated with and without inhaled corticosteroids. *Thorax* 1997;52:45-48.

22. Altman LC, Munk Z, Seltzer J, et al. A placebo controlled, dose ranging study of montelukast, a cysteinal leukotriene-receptor antagonist. *J Allergy Clin Immunol* 1998; 102: 50-56.

23. Reiss TF, Altman LC, Chervinsky P, et al. Effects of montelukast (MK-0476), a new potent cysteinyl leukotriene (LTD_4) receptor antagonist, in patients with chronic asthma. *J Allergy Clin Immunol* 1996; 98: 528-534.

24. Reiss TF, Hill JB, Harman E. Increased urinary excretion of LTE_4 after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. *Thorax* 1997; 52:1030-1035.

25. Noonan MJ, Chervinsky P, Brandon M, et al. Montelukast, a potent leukotriene receptor antagonist, causes dose-related improvements in chronic asthma. *Eur Respir J* 1998; 11:1232-1239.

26. Wenzel SE, Kamada AK. Zileuton: The first 5-Lipoxygenase inhibitor for the treatment of asthma. A*nn Pharmacother* 1996; 30: 858-864..

27. Dahlen B, Nizankowska E, Szczeklik A, et al. Benefits from adding the 5-Lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998; 157: 1187-1194.

28. Barnes NC, De Jong B, Miyamoto T. Worldwide clinical experience with the first marketed leukotriene receptor antagonist. *Chest* 1997; 111: 52S-60S.

29. Tamaoki J, Kondo M, Sakai N, et al. Leukotriene antagonist prevents exacerbation of asthma during reduction of high-dose inhaled corticosteroid. *Am J Respir Crit Med* 1997; 155: 1235-1240.

30. Okudaira H. Challenge studies of a leukotriene receptor antagonist *Chest* 1997; 111: 46S-51S.

31. Suissa S, Dennis R, Ernst P, et al. Effectiveness of the leukotriene receptor antagonist zafirlukast for mild-to-moderate asthma. *Ann Intern Med* 1997; 126: 177-183.

32. Fish J, Kemp JP, Lockey RF, et al. Zafirlukast for symptomatic mild-to-moderate asthma: A 13-week multicenter study. *Clin Ther* 1997;19: 4675-4690.

33. Knorr B, Matz J, Bernstein J, et al. Montelukast for chronic asthma in 6 to 14 year-old children. *JAMA* 1998; 279: 1181-1186.

34. Reiss T, Chervinsky P, Dockhorn R, et al. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma. *Arch Intern Med* 1998; 158: 1213-1220.

35. Leff JA, Busse WW, Pearlman D, et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise induced bronchoconstriction. *N Engl J Med* 1998; 339: 147-152.

36. Kemp JP, Dockhorn RJ, Shapiro GG, et al. Montelukast once daily inhibits exercise-induced bronchoconstriction in 6 to 14 year-old children with asthma. *J Pediatr* 1998; 133: 424-428.

37. Liu MC, Dube LM, Lancaster J, et al. Acute and chronic effects of a 5-lipoxygenase inhibitor in asthma: A 6-month randomized multicenter trial. *J Allergy Clin Immunol* 1996; 98: 859-871.

38. Israel E, Cohn J, Dube L, et al. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. *JAMA* 1996; 275: 931-936.

39. Israel E, Rubin P, Kemp JP, et al. The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma. *Ann Intern Med* 1993; 119:1059-1066.

40. Barnes NC, Pujet JC. Pranlukast, a novel leukotriene receptor antagonist: results of the first European, placebo controlled, multicentre clinical study in asthma. *Thorax* 1997; 52: 523-527.

41. Schwartz HJ, Petty T, Dube LM, et al. A randomized controlled trial comparing zileuton with theophylline in moderate asthma. *Arch Intern Med* 1998;158:141-148.

42. Laitinen LA, Naya IP, Harris A. Comparative efficacy of zafirlukast & low dose steroids in asthmatics on prn $Beta_2$-agonists. *Eur Respir J* 1997; 10 (suppl 25): 419S-420S Abstracts of the European Respiratory Society ERS Annual Congress, Berlin 20-24 Sept 1997.

43. MRL Clinical Study Report, Multicentre Study: a multicentre, double-blind, randomised, parallel group study comparing the clinical effect of MK0476 to placebo and inhaled beclomethasone.

44. MRL Clinical Study Report, Multicentre Study: a multicentre, randomised, placebo controlled, double blind, 2 period, parallel group study to assess the clinical effect of MK0476 with concommitant administration and removal of inhaled beclomethasone in asthmatic patients.

45. Accolate UK Summary of Product Characteristics 1998. Zeneca.

46. Kelloway JS, Wyatt RA, Aldis SA. Comparison of patients' compliance with prescribing oral and inhaled asthma medication. *Arch Intern Med* 1994;154:1349-52

47. Fabbri LM, Piattella M, Caramori G, et al. Oral vs inhaled asthma therapy. *Drugs* 1996; 52 (Suppl 6): 20-28.

48. Neville RG. National Attack Audit 1991 - 92. *BMJ* 1993; 306: 559-562.

49. Morbidity Statistics from General Practice 1991, OPCS Series MB5 no3.

50. Hospital Episode Statistics 1994/95, Vol 1, Department of Health.

51. eBNF 36 [CD-Rom]1994-1998 *British Medical Association & Royal Pharmaceutical Society of Great Britain* Available : BMA.

52. Buchanan A, Middleton E (1999). Additional Patient Consultations - Asthma - Generator for GPs. Prepared by PMSI UK Ltd for Merck Sharp & Dohme Limited

53. Netton A, Dennet J. 1996 Unit Costs of Health and Social Care, PSSRU, University of Kent at Canterbury.

54. Duffy R, Neville R, Hoskins G, et al. Who is admitted to hospital with asthma? *Asthma in General Practice* 1997; 5: 5-7.

55. Action Asthma. The occurrence and cost of asthma. 1990; Cambridge Medical Publications.

56. House of Commons Hansard, 24.7.97, column 577, written answers.

57. Population Trends 87 / Spring 1997, ONS.

58. Volovitz B, Faden H, Ogra PL. Release of leukotriene C4 in respiratory tract during acute viral infection. *J Pediatr* 1988;112: 218-222.

59. Mortality Statistics Series DH2 no11, ONS.

60. Rooney C, Devis T. Mortality trends by cause of death in England and Wales 1980-94: the impact of introducing automated cause coding and related changes in 1993. *Popul Trends*, Winter 1996; 86: 29-35.

61. CCOHTA. Antileukotrienes: an emerging generation of drug therapies for asthma. *Issues in emerging health technologies*; 1998: 3.

62. Montelukast and zafirlukast in asthma. *Drug Ther Bull* 1998; 36: 65-68.

63. Lipworth BJ. Modern Drug Treatment of Chronic Asthma. *BMJ* 1999; 318: 380-384.

64. The use of inhaled corticosteroids in childhood asthma. *Drug Ther Bull* 1999; 37: 73-77

Other papers published by the Trent Institute for Health Services Research are listed below:

Guidance Notes for Purchasers

96/01	Working Group on Acute Purchasing: The Use of DNase in Cystic Fibrosis (1996) by JN Payne, S Dixon, NJ Cooper and CJ McCabe.	£6.00
96/02	Working Group on Acute Purchasing: Tertiary Cardiology (1996) by J Tomlinson, J Sutton and CJ McCabe.	£6.00
96/03	Working Group on Acute Purchasing: The use of Cochlear Implantation (1996) by Q Summerfield and J Tomlinson.	£6.00
96/04	Working Group on Acute Purchasing: Statin Therapy / HMG Co-A Reductase Inhibitor Treatment in the Prevention of Coronary Heart Disease (1996) by MD Pickin, JN Payne, IU Haq, CJ McCabe, SE Ward, PR Jackson and WW Yeo.	£6.00
97/01	Working Group on Acute Purchasing: The Clinical and Cost-effectiveness of Computed Tomography in the Management of Transient Ischaemic Attack and Stroke (1997) by A Ferguson and CJ McCabe.	£10.00
97/02	Working Group on Acute Purchasing: Prostacyclin in the Treatment of Primary Pulmonary Hypertension (1997) by TW Higenbottam, SE Ward, A Brennan, CJ McCabe, RG Richards and MD Stevenson.	£10.00
97/03	Working Group on Acute Purchasing: The Use of Riluzole in the Treatment of Amyotrophic Lateral Sclerosis (Motor Neurone Disease) (1997) by J Chilcott, P Golightly, D Jefferson, CJ McCabe and S Walters.	£10.00
97/04	Working Group on Acute Purchasing: Recombinant Factor VIII Versus Plasma Derived Factor VIII in the Management of Haemophilia A: An Examination of the Costs and Consequences (1997) by C Green and RL Akehurst.	£10.00
97/05	Working Group on Acute Purchasing: The Use of Cisplatin and Paclitaxel as a First Line Treatment in Ovarian Cancer (1997) by SM Beard, R Coleman, J Radford and J Tidy.	£10.00
97/06	Working Group on Acute Purchasing: The Use of Alpha Interferon in the Management of Chronic Myeloid Leukaemia (1997) by RG Richards and CJ McCabe.	£10.00
97/07	Working Group on Acute Purchasing: Spinal Cord Stimulation in the Management of Chronic Pain (1997) by J Tomlinson, CJ McCabe and B Collett.	£10.00
97/08	Working Group on Acute Purchasing: The Use of Growth Hormone in Adults (1997) by JN Payne and RG Richards.	£5.00
97/09	Working Group on Acute Purchasing: A Review of the Use of Donepezil in the Treatment of Alzheimer's Disease (1997) by FA Pitt, J Chilcott, P Golightly, J Sykes, M Whittingham.	£10.00

97/10 Working Group on Acute Purchasing: The Use of Bone Anchored Hearing Aids (1997) by NJ Cooper, J Tomlinson and J Sutton. £10.00

98/01 Working Group on Acute Purchasing: A Review of the Use of Current Atypical Antipsychotics in the Treatment of Schizophrenia (1998) by S Beard, J Brewin, C Packham, P Rowlands, P Golightly. £10.00

98/02 Working Group on Acute Purchasing: Internal Fixation of Tibial Shaft and Distal Radius Fractures in Adults (1998) by N Calvert, P Triffit, S Johnstone, RG Richards. £10.00

99/07

98/03 Working Group on Acute Purchasing: Tacrolimus and Mycophenolate Mofetil as Maintenance Immunosuppressants following Renal Transplantation (1998) by J Chilcott, M Corchoran, K Rigg, R Burden. £10.00

98/04 Working Group on Acute Purchasing: The Effectiveness of High Dose Chemotherapy and Autologous Stem Cell Transplantation in the Treatment of Non-Hodgkin's Lymphoma and Hodgkin's Disease (1998) by S Beard, P Lorigan, A Simms, F Sampson. £10.00

98/05 Working Group on Acute Purchasing: Angiotensin-Converting Enzyme (ACE) Inhibitors in Heart failure: Reducing Mortality and Costs to the NHS (1998) by N Calvert, J Cornell, C Singleton. £10.00

98/06 Working Group on Acute Purchasing: The Use Of Ultrasound (Viability) Scans In Early Pregnancy Bleeding (1998) by N Calvert, C Singleton, P Tromans. £10.00

99/08

98/07 Working Group on Acute Purchasing: Surgery for Epilepsy (1998) by J Chilcott, C Richards, A Kemeny, S Howell. £10.00

98/08 Working Group on Acute Purchasing: The Effectiveness of High Dose Chemotherapy with Autologous Stem Cell / Bone Marrow Transplantation in the Treatment of Multiple Myeloma (1998) by S Beard, F Sampson, E Vandenberghe and F Scott. £10.00

99/05

98/09 Working Group on Acute Purchasing: Magnetic Resonance Imaging (MRI) in the Management of the Knee (1998) by S Beard and I Perez. £10.00

98/10 Working Group on Acute Purchasing: Supplementary Document: The Use of Paclitaxel in the First Line Treatment of Ovarian Cancer (1998) by S Beard, R Coleman, J Radford and J Tidy. £10.00

98/11 Working Group on Acute Purchasing: The Use of Fluoridated School Milk in the Prevention of Dental Caries (1998) by N Calvert and N Thomas. £10.00

Discussion Papers

No. 1. Patients with Minor Injuries: A Literature Review of Options for their Treatment Outside Major Accident and Emergency Departments or Occupational Health Settings (1994) by S Read. £7.00

96/01 Working Group on Acute Purchasing: The Role of Beta Interferon £7.50

	in the Treatment of Multiple Sclerosis (1996) by RG Richards, CJ McCabe, NJ Cooper, SF Paisley, A Brennan and RL Akehurst.	
96/02	The Mid-level Practitioner: A Review of the Literature on Nurse Practitioner and Physician Assistant Programmes (1996) by P Watson, N Hendey, R Dingwall, E Spencer and P Wilson.	£10.00
96/03	Evaluation of two Pharmaceutical Care Programmes for People with Mental Health Problems Living in the Community (1996) by A Aldridge, R Dingwall and P Watson.	£10.00
97/01	Working Group on Primary and Community Care Purchasing : Report of the Sub-Group on the Promotion of Quality in Primary Care - Effective Purchasing of Primary and Community Health Care: Promotion of Quality in the Provision of Primary Care (1997) by S Jennings and M Pringle.	£10.00
97/02	Working Group on Primary and Community Care Purchasing : Report of the Sub-Group on Information Needs for Health Needs Assessment and Resource Allocation (1997) by T Baxter, A Howe, C Kenny, D Meechan, M Pringle, P Redgrave, J Robinson and A Sims.	£10.00
98/01	Working Group on Primary and Community Care Purchasing : Hospital at Home - Lessons from Trent (1998) by I Perez, A Wilson, A Sims and R Harper.	£10.00

Copies of these documents are available from:-

Information Resources
Trent Institute for Health Services Research
Regent Court
30 Regent Street
SHEFFIELD S1 4DA

Tel 0114 222 0703
Fax 0114 272 4095
E-mail scharrlib@sheffield.ac.uk