The Canadian Coordinating Office for Health Technology Assessment

The Challenges of Early Assessment: Leukotriene Receptor Antagonists

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PREFACE

Systematic reviews of randomized trials combine the efficacy (and/or safety) results of individual trials to provide health care providers and others with a picture regarding the overall impact of the intervention under investigation. There are published guidelines to help ensure that appropriate methods are used for conducting and reporting systematic reviews of randomized trials.

When a “typical” systematic review is performed, a number of sources are searched including electronic databases and hand searched conference proceedings, to identify articles that might be relevant for inclusion. The typical net result is that the majority of studies included in a systematic review constitutes published individual studies. The remaining minority includes unpublished studies such as internal reports and abstracts. Detailed information from the published article about the design, population, intervention and outcomes is necessary to achieve the data synthesis of the individual studies.

When most of the literature included in a systematic review has been published (versus unpublished) it is likely that the topic is an interventions that has been in the market place for a considerable length of time (e.g. aspirin). On the other hand, retrieving unpublished trials requires several different strategies, such as contacting the manufacturers of the intervention and the authors of material found in the grey literature.a

The inclusion of unpublished studies in a systematic review, and more specifically grey literature, has recently been shown to be important in helping to reduce bias in the results of a systematic review. The exclusion of grey literature, compared to its inclusion, can exaggerate the estimates of the effectiveness of an intervention by 15% to 38%, depending on the type of grey literature. Excluding abstracts (typically the biggest single source of grey literature) results in the largest degree of bias in the systematic review.

Incomplete knowledge about the origins of unpublished literature can also bias the results of a systematic review. For example, several different abstracts might refer to the same randomized trial and this “duplication” can lead to biased estimates of the effectiveness of an intervention. Collaborating with manufacturers is an important way of minimizing or eliminating the bias associated with excluding unpublished literature and duplication.

Clarifying information in grey literature may also reduce the time delay involved in waiting until unpublished studies are published, particularly if they are statistically negative reports. Evidence suggests that there is a considerable time delay (median = 5 years) between ethics approval and the publication of statistically positive results. A longer delay exists for reports in which the results are statistically negative (median = 8 years).

The biggest challenge involved in the inclusion of abstracts in a systematic review is extracting meaningful information from the abstract. Abstracts usually contain 250 words and, as such, provide minimal information regarding the study design, population and intervention. For example, it may be difficult to ascertain the dosing schedule of the intervention or the underlying disease status of the study participants. Although most abstracts provide data on the assessment of outcomes, much important, subtle information is often not reported. For example, a measure

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a: Author reference would be added here.
of central tendency (e.g. mean) may be reported without a measure of variability, such as a standard deviation. All of this information is important, and some of it essential, if systematic reviewers are to synthesize the data in a meaningful fashion and thereby provide valid results.

One way to help resolve these problems is to establish a comprehensive dialogue between the systematic review team and those groups generating internal reports and presenting abstracts at scientific meetings. Without such a relationship it is difficult to provide meaningful information for health care providers, consumers, and policy makers regarding the (absolute or relative) utility of technologies which are new to the market or awaiting regulatory approval (“emerging technologies”).

All of the preceding points make the performance of a systematic review on an emerging technology unique. The present report, a systematic review of the efficacy and safety of leukotriene receptor antagonists (LTRAs) as compared to inhaled corticosteroids (ICs) in the treatment of mild-to-moderate chronic or recurrent asthma, exemplifies these problems.

It is important to note that, in this report, even though a direct answer to the research question was unattainable, the information retrieved in this systematic review adds to the body of evidence about the drugs in question. The review reveals that, without further information or data, it is not possible to determine the extent of LTRAs’ potential utility for mild-to-moderate asthmatics, and its use relative to inhaled corticosteroids. This finding is consistent with the recommendation put forth by the 1999 Canadian Asthma Consensus Report (CACR).

The Canadian Asthma Consensus Report states that LTRAs may be considered as an alternative to increased doses of ICs, and that LTRAs may be used as therapy adjunct to moderate or higher doses of ICs in order to achieve control of persistent asthma symptoms. This recommendation was based on level II evidence (lower quality randomized controlled trials). The Canadian Asthma Consensus Report also suggests that there is insufficient evidence to recommend LTRAs as first-line anti-inflammatory therapy in place of ICs. However, for patients who cannot or will not use ICs, LTRAs should be the primary treatment choice. This recommendation is based on level IV evidence (consensus).

In sum, when evaluating the effectiveness (and/or safety) of an emerging technology, there are some unique challenges. It is likely that many of the studies required to provide valid and reliable answers regarding effectiveness and safety will be unpublished. Without access to these sources, and without effective collaboration with the manufacturers, the internal validity of such a systematic review will be limited. As such, it is difficult for health care providers, consumers and policy makers to gain a clear picture regarding effectiveness and/or safety. These issues were faced in the present report.

These recommendations are graded according to the strength of the scientific evidence supporting it. Level I: evidence is based on randomized controlled trials (or meta-analysis of such trials) of adequate size to ensure a low risk of incorporating false-positive or false-negative results. Level II: evidence is based on randomized controlled trials that are too small to provide level I evidence. They may show either positive trends that are not statistically significant or no trends and are associated with a high risk of false-negative results. Level III: evidence is based on nonrandomized controlled or cohort studies, case series, case-control studies or cross-sectional studies. Level IV: evidence is based on the opinion of respected authorities or expert committees as indicated in published consensus conferences or guidelines. Level V: evidence is based on the opinions of those who have written and reviewed the guidelines, based on their experience, knowledge of the relevant literature and discussion with their peers.
EXECUTIVE SUMMARY

The two leukotriene receptor antagonists (LTRAs) montelukast and zafirlukast have been marketed in Canada since 1998 and 1997 respectively, for chronic use with mild-to-moderate forms of chronic or recurrent asthma in individuals at least six years of age (for montelukast) and 12 years of age (for zafirlukast). In an attempt to evaluate their possible inhaled (IC) corticosteroid-sparing utility, this systematic review discovered that the vast majority (64.6%) of evidence from 22 relevant randomized controlled trials (RCTs) were reported exclusively in abstract or conference poster form.

The present review planned to evaluate the two LTRAs’ efficacy and safety compared to that of ICs by identifying four basic definitions and concomitant research designs of their potential IC-sparing role. Three designs used LTRAs as an add-on to ICs, and the fourth placed LTRAs and ICs in a head-to-head comparison. The majority of studies fell into this last, that is, LTRA vs. IC category (64.6%), with 6 of 8 montelukast and 8 of 14 zafirlukast studies having this focus.

Certain relevance criteria had to be relaxed in order to complete the review. That is, the review’s study inclusion criteria were altered to include studies with vague or ad hoc population definitions of ‘mild-to-moderate, chronic or recurrent asthma’ or pre-trial symptom status while participants were on ICs. On the other hand, one trial inclusion criterion which could not be changed involved participants in IC-tapering studies. The minimum, symptom-controlling IC dose had to be established prior to randomization.

The preponderance of brief reports in the review necessitated requests to the drug manufacturers to resolve vague, missing or problematic information and data. Unfortunately, this information was not provided by the manufacturers. With only a considerable amount of sparse, primarily abstract-reported information at hand, the reviewers were unable to establish with any degree of confidence both the extent of the internal validity (i.e. methodological soundness) of at least 65% of the included studies and the population(s) to which even the results of these individual trials could be generalized. Without these two elements, that is, a demonstrated modicum of both methodological soundness and population-related transparency, meta-analysis was considered inappropriate. Missing, vague or problematic LTRA (i.e. intervention) and IC (i.e. control intervention) information, not to mention similarly limited efficacy and safety data, also contributed to this decision. Thus, in spite of the high quality of the employed review methods, only a qualitative synthesis of information was possible.

The overall methodological quality of this collection of clinical trials was low and, without the requested information, it was not possible to ascertain whether this state of affairs was an artifact of the publication status of trial reports (i.e. the prevalence of brief abstracts) and/or major methodological shortcomings of the studies per se.

In sum, the vast majority of the information concerning the utility of LTRAs in relation to ICs is still in progress. As such, it will likely be another few years before this information is publicly available, at which time it may be possible to fully evaluate the evidence concerning LTRAs’ value.
# TABLE OF CONTENTS

**PREFACE** .................................................................................................................................................. i

**EXECUTIVE SUMMARY** ......................................................................................................................... iii

1. **INTRODUCTION** .................................................................................................................................... 1  
   1.1 Clinical Background .......................................................................................................................... 1  
   1.2 Study Objective ............................................................................................................................... 2  
   1.3 The Research Questions .................................................................................................................. 2

2. **METHODS** ............................................................................................................................................. 4  
   2.1 Study Identification .......................................................................................................................... 4  
   2.2 Search Terms ................................................................................................................................... 4  
   2.3 Eligibility Criteria ............................................................................................................................ 4  
      2.3.1 Study Design .......................................................................................................................... 4  
      2.3.2 Population .............................................................................................................................. 4  
      2.3.3 Primary Intervention ............................................................................................................... 4  
      2.3.4 Control Intervention .............................................................................................................. 4  
      2.3.5 Outcomes ............................................................................................................................... 5  
   2.4 The Selection Process ....................................................................................................................... 5  
   2.5 Data Abstraction .............................................................................................................................. 5  
   2.6 Handling Grey Literature ............................................................................................................... 5  
   2.7 Assessment of Trial Report Quality ............................................................................................... 6

3. **RESULTS** ............................................................................................................................................... 7  
   3.1 The Need to Relax Certain Study Inclusion Criteria ....................................................................... 7  
   3.2 The Decision to Forgo Meta-analysis ............................................................................................. 7  
   3.3 Report Characteristics ..................................................................................................................... 9  
   3.4 Population Characteristics .............................................................................................................. 9  
   3.5 Intervention and Control Intervention Characteristics ................................................................... 10  
   3.6 Design Characteristics .................................................................................................................. 10  
   3.7 Trial Report Quality ....................................................................................................................... 10  
   3.8 Funding Source ............................................................................................................................. 10

4. **DISCUSSION** ....................................................................................................................................... 11

5. **CONCLUSIONS** ................................................................................................................................. 13

6. **REFERENCES** ..................................................................................................................................... 14
1. INTRODUCTION

1.1 Clinical Background

Asthma, an increasingly prevalent condition in Canada, affects over one million people of all ages.\(^1\,^2\) As such, its impact has a burgeoning human and socio-economic cost.\(^3\,^4\)

Asthma is characterized by variable obstruction of airflow associated with inflammation of the airway passages.\(^6\,^7\) The view that the care for mild-to-moderate forms of chronic or recurrent asthma should involve the direct and aggressive treatment of airway inflammation\(^6\,^9\) marked a shift starting in the mid-1980s from bronchodilator therapy to drug therapies demonstrating anti-inflammatory properties.\(^13\,^16\) Often combined with as-needed, short-acting beta\(_2\)-agonist use, the inhaled corticosteroids (ICs) have since become the cornerstone of inflammation-centred asthma care.\(^6\,^17\) The reasons for this practice include ICs’ efficacy in general as well as their tolerance and relatively rapid onset of action.\(^6\,^18\)

The mediating role of the cysteinyl leukotrienes (CysLT\(_1\)’s or ‘leukotrienes’) in the bronchoconstriction and inflammation integral to the pathophysiology of asthma has been highlighted.\(^6\,^19\) Derived from arachidonic acid by oxidative metabolism through the 5-lipoxygenase pathway,\(^20\) they have been associated with production of airway secretions, micro-vascular leakage and enhanced eosinophilic migration in the airways.\(^21\) Furthermore, at least two types of ‘inflammatory cell’ integral to the event termed asthma (e.g. eosinophils, mast cells) have been observed to produce and release leukotrienes.\(^6\) Not surprisingly then, anti-leukotrienes (ALs) have been developed as specific interventions for mild-to-moderate forms of chronic or recurrent asthma.

The two major types of AL are the leukotriene receptor antagonists (LTRAs) and the 5-lipoxygenase inhibitors (5-LOs).\(^6\) They vary in that each intervenes at a different point in the cascade of events defining asthma. The 5-LOs interfere with leukotriene production while the LTRAs are CysLT\(_1\) receptor antagonists. Three LTRAs and one 5-LO have come into varying degrees of prominence in the clinical research literature. The LTRAs include: montelukast (SINGULAIR\textsuperscript{TM}: Merck Frosst), zafirlukast (ACCOLATE\textsuperscript{TM}: AstraZeneca), and, pranlukast (ULTAIR\textsuperscript{TM}: Ono). The most widely described 5-LO has been zileuton (ZYFLO\textsuperscript{TM}: Abbott).

In spite of the perceived beneficial effects of ICs, there has been some reluctance to use these on a daily, especially long-term basis because of potential toxicities, particularly in children.\(^6\,^22\,^24\) Specific endocrine-related, adverse effects of chronic IC use have been observed, including growth suppression in children, hypothalamic-pituitary-adrenal (HPA) axis suppression, and, reduced bone mineral density.\(^6\,^25\,^30\) Moreover, these risks may be increasing since long-term IC therapy appears to be initiated increasingly sooner.\(^6\) In adults, some concern is also related to the observation that higher doses of IC are now being recommended. Moreover, there is some evidence that ICs are not completely effective in all patients. Proposed reasons for this include difficulties in targeting the relevant tissues, patient adherence to treatment and the multi-factor nature of asthma.\(^2\)

Thus, there is an increasing need to know whether or not other drugs can be used to replace ICs altogether or perhaps to reduce the IC doses required for symptom control.\(^31\) The ALs have
become possible candidates for such an IC-sparing role. Typically with a once or twice a day oral administration, the ALs have not been associated with the adverse events ascribed to long term IC use. Relative to ICs, ALs have also been touted as acting earlier in the cascade of inflammation-related events and as being more specific in their activity. On the other hand, the ALs have been associated with some evidence of adverse events as well: e.g. eosinophilic vasculitis (Churg-Strauss syndrome) and elevated hepatic enzymes.

1.2 Study Objective

The goal of this review is to evaluate the ALs’ utility relative to ICs. Of the drugs available for examination, the LTRA pranlukast and the 5-LO zileuton were excluded from the review as they are not currently marketed in Canada. Thus, montelukast and zafirlukast were the only leukotriene-centred agents included in this review (both are LTRAs). Each has been licensed for use in Canada, with montelukast and zafirlukast having gained approval for chronic use with mild-to-moderate forms of chronic or recurrent asthma in individuals at least six and 12 years of age, respectively.

1.3 The Research Questions

Four variations on the basic research question of the utility of LTRAs compared to that of ICs were defined. The intention was to address each, empirical evidence permitting. Developed as four different research designs, these questions may be described as follows:

**design ‘a’: LTRA vs. IC:** the question of LTRAs’ efficacy and safety relative to that of standard IC doses e.g. beclomethasone @ 200 µg twice a day (bid);

**design ‘b1’: IC + LTRA vs. IC + placebo:** in patients already receiving ICs, what is the impact of adding an LTRA? In this case, there is no manipulation of patients’ dose of ICs;

**design ‘b2’: IC + LTRA vs. increased IC dose + placebo:** in patients on ICs, what is the result of adding an LTRA as opposed to increasing (e.g. doubling) the IC dose?

**design ‘b3’: IC + LTRA vs. IC + placebo:** in patients on ICs, can LTRAs be added to afford tapering of the IC dose?

The three ‘b’ questions pertain to LTRAs’ potential additive effects. Certain expectations with regard to each of these questions were also established a priori by the review’s two content experts. For each of designs ‘a’ through ‘b2’, inclusive, it was expected that, prior to randomization, trial participants had been symptomatic while on ICs. For each participant in a ‘b3’ design, the minimal effective dose of ICs affording the maintenance of acceptable symptom control had to have been established prior to randomization. These four questions permit a comprehensive way to investigate the relative (to ICs) efficacy and safety of LTRAs in treating those with mild-to-moderate forms of chronic or recurrent asthma.

It was also decided to explore, where possible, the robustness of LTRAs’ impact relative to that of ICs. This involves an assessment of the strength of the evidence for any effects by the possible presence of publication bias or variations in trial quality. Publication bias is the tendency to more
readily publish statistically positive results.\textsuperscript{34} This review aimed to evaluate whether or not any effect varied on the basis of potential clinical effect modifiers of the population (e.g. age, gender) and intervention (e.g. dose) type.

An attempt was also made to translate efficacy and safety data into clinician-relevant indexes of treatment utility, that is, a number needed to treat (NNT) and a number needed to harm (NNH), respectively. Finally, the present review’s findings are discussed in light of the recent Canadian Asthma Consensus Conference’s status report and recommendations that LTRAs be used as adjunct therapy to moderate or high doses of inhaled corticosteroids.\textsuperscript{6}
2. METHODS

2.1 Study Identification
The strategy employed to identify, and eventually retrieve, citations of possible relevance to the present review involved numerous sources, including electronic databases and hand searchable documents. Details of this strategy are included in Appendix A.

2.2 Search Terms
The subject terms used in the present searches of bibliographic databases are included in Appendix A. The search strategy is in Appendix B.

2.3 Eligibility Criteria
A trial was considered eligible for inclusion only if it met each of the following criteria described in the sub-sections below.

2.3.1 Study Design: randomized, controlled trials (RCTs), with each taking the form of one of the following research designs:

‘a’: a leukotriene receptor antagonist (LTRA) vs. an inhaled corticosteroid (IC);

‘b1’: in patients on ICs, adding LTRA(s) vs. placebo (i.e. maintaining the original IC dose);

‘b2’: in patients on ICs, adding LTRA(s) vs. increasing (e.g. doubling) the IC dose;

‘b3’: in patients on ICs, adding LTRA(s) to reduce the IC dose vs. IC + placebo (i.e. maintaining the original IC dose).

2.3.2 Population: human participants who received a diagnosis of mild-to-moderate, chronic or recurrent (e.g. persistent) asthma, and where the criteria defining the parameters of this relatively broad category of ‘chronic or recurrent asthma’ were delineated a priori in the trial. For each of designs ‘a’ through ‘b2,’ inclusive, it was expected that, prior to randomization, trial participants had been symptomatic while on ICs. For each participant in a ‘b3’ design, the minimal effective dose of ICs affording the maintenance of acceptable symptom control had to have been established prior to randomization. A separate patient group includes people who have asthma triggered by exercise but this patient group is not included in the current analysis.

2.3.3 Primary Intervention: daily use of montelukast or zafirlukast for a duration of at least four weeks (with as needed short-acting beta2-agonist and/or systemic corticosteroid rescue use permitted)

2.3.4 Control Intervention: inhaled corticosteroids.
2.3.5 Outcomes: in each RCT, at least one efficacy and/or adverse event outcome (as this was very complex, the choice of outcomes is described in more detail in section 2.5 and Appendix A – Data Abstraction).

2.4 The Selection Process

After identifying the existence of trials of interest to this review, a number of phases marked the selection process. These are described in Appendix A, and include multi-reviewer ‘broad screening’ and relevance assessments (Appendix C). The process also included a validity assessment of each trial’s reported methodological quality (Appendix D). A log was kept of all activities, including any decisions to alter the protocol (section 3.1).

2.5 Data Abstraction

The data abstraction phase of the systematic review (Appendix A) involved a strategy to ensure quality control as well as one form per research focus, or design. Each form afforded capture of review-pertinent information along with data on primary, secondary and possible adverse event outcomes determined a priori by the content experts. Primary outcomes included:

- design ‘a:’ any outcome: e.g. pulmonary function, etc.;
- designs ‘b1’ & ‘b2:’ ‘number of exacerbations requiring systemic corticosteroid use;’ and,
- design ‘b3:’ ‘(%) change from baseline in required maintenance dose of ICs’ and/or ‘the final IC dose.’

2.6 Handling Grey Literature

This review revealed that a large proportion of the trial material pertinent to the present project took the form of abstracts or conference posters (section 3.3 and Appendix F). These constitute examples of grey literature, that is, reports “that are unpublished, have limited distribution, and are not included in bibliographic retrieval systems” (Table 1). The incorporation of grey literature data into meta-analysis appears to be quite important, providing that sufficient published data has been included. McAuley et al. recently found that, on average, and relative to its inclusion, the exclusion of grey literature resulted in a statistically significant overestimate of the effectiveness of an intervention by 38%. The chances of finding a significant result may increase when grey literature is excluded from meta-analysis.

Certain shortcomings were recognized in many of the present review’s relevant LTRA trial reports especially in the grey literature reports. These failings included missing, vague or problematic details (Tables 1 through 4). For example, one trial abstract reported two different sample size estimates without clarification of the discrepancy.

To help overcome these limitations, the reviewers contacted the Canadian headquarters of the pharmaceutical companies responsible for funding the trials. The aim was to solicit specific study details required to: (a) identify which individual reports referred to a given trial; (b) allow an evaluation of the trials’ internal validity (i.e. trial methodological quality); (c) derive a
qualitative picture of the employed outcomes; (d) inform a possible meta-analysis, including an
investigation of the impact on estimates of efficacy of publication bias and methodological
quality, for example; and (e) permit the meaningful generalizability of the review’s qualitative
and quantitative results.

However, to date, the aforementioned issues have not been resolved as the pharmaceutical
companies did not supply the details requested. Meta-analysis was thus considered inappropriate
(section 3.2 and Appendix E). At most, some direction was received about whether or not certain
reports referred to the same trial. A companion report\textsuperscript{39} to a Reiss document\textsuperscript{40} (Table 1) was
never retrieved, however.

2.7 Assessment of Trial Report Quality

Trial report quality was evaluated by two experienced, independent raters who used a validated,
three-item scale and an index of the concealment of treatment allocation (Appendix D). The
former assesses randomization (0-2 points), double-blinding (0-2 points), and the description of
withdrawals and dropouts (0-1 point).\textsuperscript{41} Allocation concealment can be considered adequate,
inadequate or unclear.\textsuperscript{42} All inter-rater disagreements were resolved by consensus.

What follows are the major findings of this review. The first two sections (3.1 and 3.2) establish
evidence for the significant limitations on the internal validity and generalizability of the
remaining observations (sections 3.3 - 3.8).
3. RESULTS

3.1 The Need to Relax Certain Study Inclusion Criteria

In undertaking the relevance assessment, it was realized that unless two criteria were relaxed somewhat, the review might not even yield a qualitative synthesis. First, while it was established by the content experts that the parameters defining ‘mild-to-moderate, chronic or recurrent asthma’ should have been defined a priori by trialists in order to be included in the present review, it appears that in many cases the trials’ selection requirements were poorly delineated, if at all (e.g. ICs-free patients\textsuperscript{43}). In some cases it was also impossible to tell from a report whether laboratory values in the report reflected a priori trial selection criteria or were an a posteriori summary of the baseline descriptive characteristics of the randomized sample.\textsuperscript{44, 45} These shortcomings are probably due to the obligatory reliance on abstracts for this review and space limitations in a 250 word abstract. As a result, the protocol was changed. Reports were now considered relevant even if vague or ad hoc definitions of ‘mild-to-moderate, chronic or recurrent asthma’ had been used to describe the trial populations.

The content experts had also determined a priori another inclusion condition which had to be relaxed to allow this review to be completed. That is, for each research focus (i.e. designs ‘a,’ ‘b1,’ ‘b2,’ ‘b3’), there was an expectation that there would be unequivocal information in each report pertaining to trial participants’ pre-trial symptom status while on ICs. For example, it had been agreed upon that participants in all designs except ‘b3’ should have been selected on the basis of being symptomatic while on pre-trial doses of IC. However, not all reports provided unambiguous evidence that their trial participants had been selected on this basis.\textsuperscript{43} One ‘a’ design trial\textsuperscript{44, 45} included ‘stable asthmatics’ without defining what this term meant. As a result, this criterion had to be relaxed in order to complete the review. Studies with participants merely receiving a diagnosis of ‘mild-to-moderate, chronic or recurrent asthma’ symptomatology were included.

On the other hand, one requirement that could not be modified pertained to the ‘b3’ (i.e. IC-tapering) design. That is, without the establishment of the minimal effective (i.e. symptom-controlling) IC dose prior to randomization, results from a trial with a drug-tapering rationale would likely be meaningless. At least one trial report\textsuperscript{46} had to be excluded because it could not be confirmed that this criterion had been met (section 3.3 and Appendix F).

3.2 The Decision to Forego Meta-analysis

While both are LTRAs, montelukast and zafirlukast are different drugs with divergent doses and dosing schedules (Table 1). In addition, this review noted variability in the identity of the ICs established as contrasts against which evidence for LTRAs’ relative efficacy and safety was assumed to be observable (Tables 1 and 3). Third, four different research questions regarding LTRAs’ value relative to that of ICs (Table 1) had been posed in this review yet the results from the various designs could not be considered comparable. These three circumstances alone severely limited the potential to pool data across different designs and for the same drug (e.g. montelukast ‘a’ vs. montelukast ‘b3’ designs) or across the two drugs within a single design (e.g. montelukast ‘a’ vs. zafirlukast ‘a’ designs).
An additional complication was that for each of the four research designs in this review, many different outcomes were employed, thereby limiting comparability (Figure 2). This state of affairs can be illustrated by the variable utilization of, and reporting of data for primary outcomes in these trials.

In Appendix E, each research focus is evaluated in turn, including the evidence pertaining to the validity of pooling primary outcome results from the selected trials. Secondary and adverse event outcomes are then assessed with reference to the possibility of pooling their data. To briefly summarize these observations; without the clarifying information from the pharmaceutical companies, it was impossible to resolve the situations wherein information or data were missing, vague, or problematic, particularly in the 14 (of 22) studies presented exclusively in brief, grey literature reports.

It was not possible, however, to use only journal-published reports. Three published trials evaluated zafirlukast, and two of these involved an ‘a’ design (Table 1). On the basis of key trial specifications (i.e. intervention, population, outcome), one of these two studies was found to be similar to two, grey literature-reported investigations also included in the review. Since clarification of the exact nature of their overlap was unavailable, and in spite of some commonly employed outcomes, the Bleecker and Kim trials’ data could not be synthesized quantitatively.

Of the five published trials concerning the study of montelukast, two studies (i.e. an ‘a’ and a ‘b1’ design) were actually presented in a single publication (Table 1). Yet, while 60% (3/5) of the published trials entailed ‘a’ designs, only two of these three studies employed some of the same outcomes (Figure 2).

Overall, the lack of confidence in many of the details contained in a number of trial reports made it impossible to collectively or individually assess the internal validity of the selected studies or to clearly establish the population(s) to which results could be generalized. Descriptions of key population characteristics as basic as age and gender were missing (section 3.4 and Appendix G; Tables 1 and 2), as were unequivocal descriptions of trial participants’ pre-trial symptom status while on ICs (e.g. well-controlled vs. symptomatic) (section 3.1). Moreover, not all studies sharing the same research focus (i.e. design) included participants with the same a priori and/or actual baseline, clinical and laboratory definitions of ‘mild-to-moderate, chronic or recurrent asthma’ (section 3.1).

Yet, these situations also arose against the backdrop of the decision by the content experts to evaluate trials having enrolled individuals falling into what might be considered a relatively broad range of types (i.e. severities) of chronic or recurrent asthma patient. Hence, in defining the disease criterion as ‘mild-to-moderate’ forms of chronic or recurrent asthma, the possibility emerged that this systematic review included studies collectively specifying either a broadly- and ill-defined study population, many different populations, or some combination thereof. Without the verification of especially grey literature reported details, there could be no way to determine the correct interpretation.
The correctness or specificity of other information was limited as well. For example, certain intervention characteristics were never made explicit (Tables 1 and 3). On more than one occasion, the exact type(s) of IC and dose could not be determined from an abstract report. There was thus no means by which to ascertain the degree of comparability of the individual trials within each type of research focus (i.e. designs ‘a’ through ‘b3’).

Therefore, in light of the combined weight of the limitations, a meta-analysis was ruled out. Likewise, the aim to derive clinician-oriented NNT (number-needed-to-treat) or NNH (number-needed-to-harm) as well as to assess the role of publication bias and other effect modifiers (e.g. trial report quality) as possible influences on estimates of efficacy or safety could not be undertaken. Only a qualitative synthesis of the respective studies’ parameters was considered appropriate at this time, and these summary findings need to be interpreted with caution.

3.3 Report Characteristics

A detailed description of the report characteristics, including reasons for excluding reports, may be found in Appendix F. What follows is a brief summary.

A total of 185 reports were deemed potentially relevant for the present review (Figure 1). The selection process ultimately yielded 43 trial reports described in 41 unique documents, and from which 22 unique trials were identified. Only eight trials (36.4%) were described by published documents (Table 3). Some studies were described by more than one report, and study identifications reflect this reality (Table 1: e.g. 52-56). Moreover, in each of two cases, a report described two trials. Keeping at hand all of a study’s reports was intended to make available as much detail as possible from all sources to afford valid ratings of trial methods quality.

3.4 Population Characteristics

Individual trial information concerning population characteristics and summaries thereof, are captured in Tables 1 and 2, respectively. Not all studies provided compilable data, however.

In total there were approximately 6,971 patients included in this review of 22 trials (Table 2). A discrepancy in sample size description occurred in the documents reporting one study of montelukast. Only 19 trials provided extractable sample size data, however. The mean sample size of all studies was thus approximately 367 participants. The trials’ sample sizes ranged from nine to 1,282 individuals.

The mean age of all study participants was not calculated because only six of 22 trial report collections fully described sample age information. The age range of trial participants for the 13 trials reporting such information was six to 85 years of age. Where data were reported, the median ‘percent male’ composition of included trials (n = 10) was 48.9%. Additional breakdowns of data by LTRA type for sample size, age and gender are presented in Appendix G.
3.5 Intervention and Control Intervention Characteristics

Each of the included trials investigated the efficacy and/or safety of LTRAs compared to that of ICs (Table 1). For all trials (n = 22), interventions lasted, on average, 11.7 weeks (range: 4 to 39 weeks) (Table 3). On average, montelukast trials (mean: 15.6 weeks; range of 4 to 39 weeks; n = 8) lasted longer than zafirlukast ones (mean: 9.2 weeks; range of 4 to 13 weeks; n = 14). Details concerning intervention and control intervention characteristics broken down by type of LTRA are provided in Appendix H.

3.6 Design Characteristics

Most trials investigated questions of LTRAs’ efficacy and safety when compared directly to ICs (i.e. ‘a’ design), and via parallel research designs. Details concerning the designs employed in the trials included in the present review are contained in Appendix I as well as in Tables 1 and 2 (Column 1).

3.7 Trial Report Quality

Overall, the methodological quality of trials as evaluated through report documents was low. Details are reported in Appendix J as well as Tables 1 and 4.

3.8 Funding Source

All of the montelukast trials were funded at least in part by its manufacturer, Merck Frosst (Table 4). On the other hand, and excluding the Johnson, et al, 1999 report, five of the 14 zafirlukast trials were supported by GlaxoWellcome. The rest were sponsored by AstraZeneca. All of the GlaxoWellcome-funded, ‘a’ design studies likely employed fluticasone as the primary intervention.
4. DISCUSSION

The primary goal of this review was to determine the efficacy and safety of the LTRAs’ montelukast and zafirlukast as compared to ICs in the treatment of mild-to-moderate forms of chronic or recurrent asthma. (This excluded other potential foci such as the potential utility of LTRAs to treat exercise-induced asthma, for example.) However, difficulties characterizing both the relevant literature and the retrieval of important clarifying information and data precluded a meta-analysis. Therefore, qualitative results reported here cannot be interpreted as supporting either of the views that the two LTRAs do or do not constitute a clear clinical advancement as IC-sparing interventions. No definitive answer was derivable regarding LTRAs’ potential as an alternative or as an add-on to ICs.

For a number of reasons it is unlikely that the present collection of efficacy results could represent a bias-free picture of LTRAs’ clinical value relative to ICs. First, one key facet of trial quality was found to be extremely problematic in this set of studies. Not one trial could be characterized as having unequivocally exhibited adequate allocation concealment. This is an important observation because, at the meta-analysis level of observation, low trial quality has been found to be associated with exaggerated estimates of treatment effectiveness. This suggests the possibility that a pooled point estimate of efficacy derived from the present collection of trials could constitute either an overestimate or an underestimate of LTRAs’ true benefit.

Secondly, most of the trials included in the review were described by grey literature documents whose exclusion from meta-analyses has been observed to produce overestimates of treatment effectiveness. This suggests the possibility that a pooled point estimate of efficacy derived from the results of the present collection of predominantly grey literature described trials could constitute an underestimate of LTRAs’ true benefit.

The results of this systematic review point to some general methodological problems when attempting to evaluate the effectiveness of an ‘emerging technology.’ In this instance, the question has been whether, when compared to ICs as the standard therapy, LTRAs as the newer intervention can: (1) lead to improved symptoms, pulmonary function, airway inflammation and nonspecific bronchial hyperreactivity; (2) decrease exacerbation rates; (3) produce minimal side effects; (4) be easy to take; (5) be used to treat ‘all comers’ with mild-to-moderate forms of chronic or recurrent asthma; and (6) improve long-term outcomes of the disease. The present review concerned itself with items 1, 2 and 3.

In general, when conducting a systematic review the reviewer faces a situation whereby the majority of the evidence is available in a published format, such as a peer reviewed publication. The remainder of the evidence is then sought through a variety of other approaches. These include: extensive searches of databases containing grey literature; hand searching conference proceedings; and, contacting experts both in the content area and industry. In the present undertaking, however, the reviewers faced the opposite situation. Here the minority of information was available in published format while the majority of the evidence was available in grey literature form (e.g. abstracts). Only 36.4% (8/22) of the unique trials had information or data drawn from a journal-published document. This had a significant impact on the review.
An assessment of what was contained in the grey literature report documents constituting the remaining 63.6% (14/22) of the trials showed that much of the information necessary to establish a context from within which to generalize study results was missing, vague, or conflicting across even multiple reports referring to the same trial. Moreover, few of the studies had employed the primary outcomes deemed clinically significant by the content experts. Thus, it was impossible to tell whether, for example, low methodological quality was a function of the publication status of the documents (i.e. mostly brief reports) and/or major methodological shortcomings inherent in the trials themselves.

While recent evidence suggests the importance of including grey literature in meta-analyses of intervention effectiveness, this review included a disproportionate number of such reports. However, the clarifying information was not obtainable from the manufacturers, and this contributed to the present reviewers’ inability to perform a more in-depth systematic review and possible meta-analysis.

Recent evidence has suggested that there is a considerable time delay (median = 4.7 years) between ethics approval and the publication of statistically positive results. This delay is increased for reports in which the results are statistically negative (median = 8 years). It may thus take up to eight years for clinical trial information to become publicly available and to allow systematic reviewers to fully evaluate the merits of a new health technology, for example.

If these figures are generally representative, then individuals doing future reviews of emerging health technologies may often run into the same situation faced by the present review team. With reviews often initiated soon after a new health technology moves into the professional and/or public spotlight, many reviewers are likely to complete their reviews before trialists have published their results. Grey literature reports will probably constitute the source most frequently tapped to extract trial information and data. Furthermore, given the previously mentioned timelines on getting papers published, these reviewers will be even less likely to find published documents reporting statistically negative results.

Overall, this means that the confidence in the validity of the grey literature derived results within the review of a new health technology may be limited. This also signifies that, like the present review investigating LTRAs as compared to ICs, the delivery to the professional and public communities of results from a valid evidence-based appraisal will be delayed until trial method information and results are provided in a timely fashion by those in charge of these trials.
5. CONCLUSIONS

The circumstances surrounding the present review have made it inappropriate to provide guidance concerning the relative (to ICs) utility of the two LTRAs for clinicians, for potential recipients of LTRAs within clinical case management and clinical research settings, for policymakers.

The results of the qualitative summaries of information concerning population, intervention, and trial method characteristics are sufficiently problematic to preclude their generalizability. The missing, limited or suspect population characteristic information which contributed to the decision to relax some relevance criteria to allow completion of this review, has yielded an unclear sense as to whom the results would pertain when seen collectively and, much more often than not, on an individual trial basis as well. Finally, the inability to thoroughly assess the internal validity of each of the included trials, precluded an unequivocal appreciation of the collective and most of the individual trial estimates of the value of LTRAs as compared to ICs.

At this time, it may be concluded that the collective evidence for the two LTRAs’ efficacy and safety has yet to be answered in a satisfactory fashion. This has precluded determining their exact clinical value as monotherapy, let alone as an adjunct to moderate or high doses of ICs as was recently recommended.6

Finally, likely the only other certainty highlighted by this review is the need to institute mechanisms by which to ensure the full and timely public disclosure of pertinent trial information and results to permit their evaluation by the public from whom the original trial participants were drawn, practitioners and any third parties charged with estimating the weight of all of the evidence concerning the value of any, especially emerging, health technology.
6. REFERENCES


17. Ducharme FM, Hicks GC. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma. *Cochrane Database Syst Rev* 2000;(3):CD002314.


56. Skalky CS, Edelman JM, Polis A, Bird S, Gormley GJ, Israel E. Montelukast sodium (MK) compared to inhaled beclomethasone diproprionate (BD) in adult asthmatics: a


Jones PW, Silverman S, Naya IP, Harris A. Greater improvements in QOL (Quality of Life) over 12 months with zafirlukast 20 mg bd plus low dose steroids versus double dose steroids in patients with greater QOL improvement [abstract]. *Eur Respir J* 1999:Abstract P2289.


7. FIGURES AND TABLES
FIGURE 1: Progress Through the Various Stages of the Review

Potentially relevant RCT reports identified and screened for retrieval (n = 185)

- Reports excluded, with reasons (n = 125):
  a. not a human study (n = 2); b. indication other than asthma (n = 3); c. primary intervention other than montelukast or zafirlukast (n = 36); d. did not include ICs as ‘control’ (n = 27); e. not an RCT (n = 19); f. LTRA intervention < 4 weeks (n = 12); g. design outside the scope of the present review (n = 22); h. review (n = 3); & i. never retrieved (n = 1)

- Reports retrieved for more detailed evaluation (n = 60)

- Reports excluded, with reasons (n = 17):
  a. not an RCT (n = 3); b. LTRA intervention lasted < 4 weeks (n = 12); & c. a ‘b3’ design study did not indicate unequivocally that the minimal effective dose of ICs had been established prior to randomization (n = 2)

Potentially appropriate RCTs to be included in the meta-analysis (n = 22)*

- RCTs included in meta-analysis (n = 0)

- RCTs excluded from the meta-analysis, with reasons (n = 22):
  e.g. limited or problematic primary outcome data

- RCTs with usable information, by outcome (n = n/a)

- RCTs withdrawn, by outcome, with reasons (n = n/a)

**KEY:**

IC= inhaled corticosteroid
LTRA= leukotriene receptor antagonist
RCT= randomized controlled trial
n/a= not applicable

*Note that more than one report can refer to a given trial (see Table 1) and the 22 unique trials are described by 44 reports.
FIGURE 2: Data-centered Restrictions on the Ability to Undertake a Meta-analysis

F2.1 Variability in Primary Outcomes; each reported to have been employed in more than one ‘a’ design study of montelukast:

1. AM PEF (change from baseline):\textsuperscript{39,40,47-50} of three reports, one of the two published trials presented problematic data (e.g. means); the second published paper contained anomalous standard deviations; and the single grey-literature-described-trial included no data.

2. PM PEF (change from baseline):\textsuperscript{39,40,47-50} of three reports, there were no montelukast data from a published paper; no standard deviations within a second published paper; and the single grey-literature-described-trial included no data.

3. $\beta_2$-agonist use (# of patients):\textsuperscript{52,56} of two studies described by grey literature documents, neither reported data.

4. $\beta_2$-agonist rescue (percent change from baseline in mean daily use):\textsuperscript{47,48,53-55} of two reports, one published paper likely reported anomalous standard deviations; and the single grey-literature-described-trial included unusable sample size information.

5. Nights without awakenings due to asthma symptoms:\textsuperscript{39,40,52,56} of two trials described by three grey literature reports (i.e. two reports referring to the same trial), none included data; and there was no clear indication of the units used to express the outcome data.

6. Physician’s global evaluation of overall change (mean):\textsuperscript{49,50,53-55} of two documents, there were no extractable data from a published paper; and no usable sample size information was reported in the grey-literature-described-trial.

7. Patient’s global evaluation:\textsuperscript{47,48,53-55} of two trials, one published paper did not present montelukast data; no usable sample size information was reported in the grey-literature-described-trial; and there was no indication of the units used to express the outcome data.

8. Systemic corticosteroid rescue (# patients):\textsuperscript{39,40,56} of two grey-literature-described-trials, one had conflicting sample size data.

9. Daytime asthma symptoms score (change from baseline):\textsuperscript{39,40,47-50} of three reports, one published paper reported anomalous standard deviations; one published trial presented problematic data (e.g. means); and only the grey-literature-described-study presented data.

10. Patients without asthma attack (%):\textsuperscript{49,50,53-55} of two reports, with one published, the grey-literature-described-trial document contained no usable sample size data.

11. Asthma exacerbations (% days):\textsuperscript{47-50} of two published papers, one reported no montelukast data.
12. FEV\textsubscript{1} (percent change from baseline):\textsuperscript{38-40,47-50} of two published papers and two grey-literature-described-trials, one published trial presented problematic data (e.g. means); and the data from the two grey-literature-described-trials were unverified.

13. FEV\textsubscript{1} (change from baseline):\textsuperscript{47,48,53-56} two of the three reports (both referring to the same trial) were unverified grey-literature-described-trials.

14. Asthma control days (%):\textsuperscript{49,50,52-56} three of the four reports (all three referring to the same trial) were unverified grey-literature-described-trials.

F2.2 Primary Outcomes; each reported to have been employed in more than one ‘a’ design study of zafirlukast:

1. FEV\textsubscript{1} (change from baseline):\textsuperscript{58,59,66-69} of three grey-literature-described-trials, one presented no standard deviation data and another presented neither usable sample size information nor standard deviations.

2. AM PEF (change from baseline):\textsuperscript{43,58,59,65-69} of five grey-literature-described-trials, three reported no usable sample size information and/or no standard deviations.

3. PM PEF (change from baseline):\textsuperscript{58,59,65,66} of three grey-literature-described-trials, one reported no standard deviations and another, no usable sample size information.

4. Patient preference (%):\textsuperscript{44,45,70} of two grey-literature-described-trials, one reported no usable sample size information.

F2.3 Adverse Event Outcomes; each reported to have been employed in more than one ‘a’ design study of montelukast:

1. Withdrawals due to adverse effects:\textsuperscript{47,48,53-55} of two RCTs, with one published, the grey-literature-described-trial included no IC data; and there was no indication of the units used to express the adverse event data.

2. Withdrawals due to poor asthma control (# exacerbations):\textsuperscript{39,40,47-50} of three trials, a single published one reported problematic data (e.g. means); and one trial was described by grey literature.

3. Frequency of adverse experiences:\textsuperscript{53-56} both reports referred to the same trial and were grey literature documents; and there was no indication of the units used to express the outcome data.
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<th>Author</th>
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<th>N (total/ contrast)</th>
<th>Age: Mean (sd), Range</th>
<th>Gender (% male)</th>
<th>Design</th>
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<th>IC Dose/ schedule</th>
<th>Intervention Length</th>
<th>Publication status</th>
<th>Funded by</th>
<th>Quality/ Allocation Concealment</th>
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<td>642/ 401</td>
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<td>FLU 88 ug bid; BUD 200 ug bid</td>
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<td>BCM 200 ug bid + PB tablet</td>
<td>PB + BCM 200 ug bid = 16 wks; M 10 mg + PB (after blind BCM removal) = 12 wks; data compared over last 10 wks</td>
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<td>1999</td>
<td>224/ 224 437/ 437</td>
<td>NR (NR), ≥12 yrs 34.2 (NR) yrs, 12-81 yrs</td>
<td>NR (&lt;100%) 40%</td>
<td>a</td>
<td>Zf 20 mg bid</td>
<td>FLU 88 ug bid</td>
<td>12 wks</td>
<td>Abstract</td>
<td>Glaxo Wellcome</td>
<td>3/UNC</td>
</tr>
<tr>
<td>82</td>
<td>Kim</td>
<td>2000</td>
<td>224/ 224 437/ 437</td>
<td>NR (NR), ≥12 yrs 34.2 (NR) yrs, 12-81 yrs</td>
<td>NR (&lt;100%) 40%</td>
<td>a</td>
<td>Zf 20 mg bid</td>
<td>FLU 88 ug bid</td>
<td>6 wks</td>
<td>Journal article</td>
<td>Glaxo Wellcome</td>
<td>4/UNC</td>
</tr>
<tr>
<td>67</td>
<td>Rickard Stanford Carranza- Rosenzweig</td>
<td>1999</td>
<td>224/ 224 437/ 437</td>
<td>NR (NR), ≥12 yrs 34.2 (NR) yrs, 12-81 yrs</td>
<td>NR (&lt;100%) 40%</td>
<td>a</td>
<td>Zf 20 mg bid</td>
<td>FLU 88 ug bid</td>
<td>6 wks</td>
<td>Abstract/ Abstract/ Abstract</td>
<td>Glaxo Wellcome</td>
<td>4/UNC</td>
</tr>
<tr>
<td>66</td>
<td>Laitinen</td>
<td>1997</td>
<td>481/ 481 437/ 437</td>
<td>NR (NR), 12-69 yrs 34.2 (NR) yrs, 12-81 yrs</td>
<td>NR</td>
<td>a</td>
<td>Zf 20 mg bid; Zf 80 mg bid</td>
<td>BCM 200-250 ug bid</td>
<td>6 wks</td>
<td>Abstract</td>
<td>Astra Zeneca</td>
<td>1/UNC</td>
</tr>
<tr>
<td>44</td>
<td>Ringdal* Ringdal</td>
<td>1998</td>
<td>167/ 167 437/ 437</td>
<td>NR (NR), NR 12-69 yrs 34.2 (NR) yrs, 12-81 yrs</td>
<td>NR</td>
<td>a</td>
<td>Zf 20 mg bid</td>
<td>BCM 200-250 ug bid</td>
<td>4 wks</td>
<td>Abstract/ Abstract</td>
<td>Astra Zeneca</td>
<td>1/UNC</td>
</tr>
<tr>
<td>70</td>
<td>Weinberg</td>
<td>1998</td>
<td>132/ 132 437/ 437</td>
<td>NR (NR), 12-17 yrs 34.2 (NR) yrs, 12-81 yrs</td>
<td>50.0%</td>
<td>a</td>
<td>Zf 20 mg bid</td>
<td>BCM 100-200 ug bid</td>
<td>4 wks</td>
<td>Abstract</td>
<td>Astra Zeneca</td>
<td>1/UNC</td>
</tr>
<tr>
<td>80</td>
<td>Virchow</td>
<td>1998</td>
<td>368/ 368 437/ 437</td>
<td>48.3 (12.8) yrs, 17-71 yrs 34.2 (NR) yrs, 12-81 yrs</td>
<td>50.5%</td>
<td>b1</td>
<td>Zf 20 mg bid + (IC 1000-4000 ug/day of BCM, BUD, or FLU) PB + (IC 1000-4000 ug/day of BCM, BUD, or FLU)</td>
<td>6 wks</td>
<td>Journal article/ Abstract/ Abstract/ Abstract</td>
<td>Astra Zeneca</td>
<td>3/UNC</td>
<td></td>
</tr>
<tr>
<td>74</td>
<td>Jones</td>
<td>1999</td>
<td>NR/ NR 437/ 437</td>
<td>NR (NR), NR</td>
<td>NR</td>
<td>b2</td>
<td>Zf 20 mg bid + ICs (undefined) 400-500 ug/day; Zf 80 mg bid + ICs (undefined) 400-500 ug/day</td>
<td>ICs (undefined) 800-1000 ug/day</td>
<td>first 12 wks</td>
<td>Abstract</td>
<td>Astra Zeneca</td>
<td>2/UNC</td>
</tr>
<tr>
<td>75</td>
<td>Nayak Nayak</td>
<td>1998</td>
<td>394/ 394 437/ 437</td>
<td>NR (NR), ≥12 yrs</td>
<td>NR</td>
<td>b2</td>
<td>Zf 40 mg bid + BCM 336 ug/day; Zf 80 mg bid + BCM 336 ug/day</td>
<td>BCM 672 ug/day + PB</td>
<td>13 wks</td>
<td>Abstract/ Poster</td>
<td>Astra Zeneca</td>
<td>3/UNC</td>
</tr>
<tr>
<td>Ref</td>
<td>Author</td>
<td>YEAR</td>
<td>N* (total/ contrast)</td>
<td>Age: Mean (sd), Range</td>
<td>Gender (% male)</td>
<td>Design</td>
<td>LTRA Dose/ schedule</td>
<td>IC Dose/ schedule</td>
<td>Intervention length</td>
<td>Publication status</td>
<td>Funded by</td>
<td>Quality/ Allocation Concealment</td>
</tr>
<tr>
<td>-----</td>
<td>--------</td>
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<td>--------------------------------</td>
</tr>
<tr>
<td>77</td>
<td>Ringdal</td>
<td>1997-1999</td>
<td>440/ 440</td>
<td>NR (NR), ≥ 12 yrs</td>
<td>NR</td>
<td>b2</td>
<td>Zf 20 mg bid + BCM 400-500 ug/day; Zf 80 mg bid + BCM 400-500 ug/day</td>
<td>BCM 800-1000 ug/day + PB</td>
<td>12 wks</td>
<td>Abstract</td>
<td>AstraZeneca</td>
<td>3/UNC</td>
</tr>
<tr>
<td>78</td>
<td>Laitinen</td>
<td>1995</td>
<td>262/ 262</td>
<td>NR (NR), NR</td>
<td>NR</td>
<td>b3</td>
<td>Zf 20 mg bid + ICs (undefined) 800-2000 ug/day</td>
<td>ICs (undefined) + PB</td>
<td>12 wks</td>
<td>Abstract</td>
<td>AstraZeneca</td>
<td>2/UNC</td>
</tr>
<tr>
<td>79</td>
<td>Micheletto</td>
<td>1997</td>
<td>9/ 9</td>
<td>NR (NR), 28-55 yrs</td>
<td>44.4%</td>
<td>b3</td>
<td>Zf 20 mg bid + BCM 1500 ug/day</td>
<td>BCM 1500 ug/day + PB</td>
<td>12 wks</td>
<td>Abstract</td>
<td>AstraZeneca</td>
<td>5/UNC</td>
</tr>
</tbody>
</table>

**Key:**

LTRA = leukotriene receptor antagonist; IC = inhaled corticosteroid; Ref = reference list #

Author\textsuperscript{1} = will use these, combined U.S. & international data in all summaries; Author\textsuperscript{2} = international data; Author\textsuperscript{3} = U.S. data; Author\textsuperscript{4} = never received a copy requested from pharmaceutical company; Author\textsuperscript{*} = these reports have been confirmed by the pharmaceutical company as referring to the same RCT; Author\textsuperscript{**} = never received confirmation from pharmaceutical company re its possible overlap with Johnson/Bowers (1998), and thus, Johnson (1999) information is excluded from summaries of characteristics: Tables 2 to 4);

N* = first n refers to total sample and second n excludes subjects receiving intervention(s) outside the specific contrast being studied (e.g. placebo in an ‘a’ design);

contrast = the specific contrast deemed relevant for the present review (e.g. LTRA vs IC in an ‘a’ design)

\textsuperscript{sd} = standard deviation; \textsuperscript{med} = median; \textsuperscript{NR} = not reported; \textsuperscript{PB} = placebo; \textsuperscript{db} = double blind; \textsuperscript{O} = overall sample information/data; \textsuperscript{Oc} = calculated overall sample value(s)

\textsuperscript{M} = Montelukast (Merck); \textsuperscript{Zf} = Zafirlukast (AstraZeneca);

BCM = Beclomethasone, an inhaled IC; FLU = Fluticasone, an inhaled IC; BUD = Budesonide, an inhaled IC

Design\textsuperscript{a} = LTRA vs. IC in symptomatic pts; Design\textsuperscript{b1} = LTRA as add-on to IC vs. IC alone in symptomatic pts; Design\textsuperscript{b2} = LTRA as add-on to IC vs. increasing IC in symptomatic pts; Design\textsuperscript{b3} = LTRA as add-on to IC vs. IC alone in well-controlled pts, with tapering of IC as primary objective (yet where minimal effective IC dose was sought prior to randomization);

**** given multiple quality ratings per trial, used highest score for each of total quality and allocation concealment in summary tables

\textsuperscript{od} = once daily; \textsuperscript{bid} = twice daily; \textsuperscript{hs} = at bedtime; \textsuperscript{tid} = three times daily

\textsuperscript{mo} = month; \textsuperscript{wks} = weeks

Quality = trial report quality; UNC = Unclear allocation concealment
### TABLE 2: Summary of Reported Population Characteristics† †see Appendix G

<table>
<thead>
<tr>
<th>Montelukast: All designs (n = 8 trials)</th>
<th>Median mean age; range (years)</th>
<th>Trials known definitively to have focused exclusively on children (C) or adolescents (A) (%)</th>
<th>Trials likely to have included some adolescents in their sample (%)</th>
<th>Median % male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast: Design 'a' (n = 6)</td>
<td>30.2 yrs (n = 1); 6-85 yrs (n = 5)</td>
<td>C = 16.7% (1/6); A = 0</td>
<td>75.0% (3/4)</td>
<td>37.5% (n = 3)</td>
</tr>
<tr>
<td>Montelukast: Design 'b1' (n = 1)</td>
<td>15-78 yrs (n = 1)</td>
<td>C = 0</td>
<td>100% (1/1)</td>
<td>54.0% (n = 1)</td>
</tr>
<tr>
<td>Montelukast: Design 'b2' (n = 0)</td>
<td>40.5 yrs (n = 1); 16-70 yrs (n = 1)</td>
<td>C = 0</td>
<td>100% (1/1)</td>
<td>47.8% (n = 1)</td>
</tr>
<tr>
<td>Montelukast: Design 'b3' (n = 1)</td>
<td>34.2 yrs (n = 1)</td>
<td>C = 0</td>
<td>100% (1/1)</td>
<td>47.8% (n = 1)</td>
</tr>
<tr>
<td>Zafirlukast: All designs (n = 14)</td>
<td>34.2 yrs (n = 3); 12-81 yrs (n = 3)</td>
<td>C = 0; A = 28.6% (4/14)*</td>
<td>57.1% (8/14)</td>
<td>50.0% (n = 5)</td>
</tr>
<tr>
<td>Zafirlukast: Design 'a' (n = 8)</td>
<td>31/34.2 yrs (n = 2); 12-81 yrs (n = 2)</td>
<td>C = 0</td>
<td>75% (6/8)</td>
<td>50.0% (n = 3)</td>
</tr>
<tr>
<td>Zafirlukast: Design 'b1' (n = 1)</td>
<td>48.3 yrs; 17-71 yrs (n = 1)</td>
<td>C = 0</td>
<td>100% (1/1)</td>
<td>50.5% (n = 1)</td>
</tr>
<tr>
<td>Zafirlukast: Design 'b2' (n = 3)</td>
<td>NR; ≥ 12 yrs (n = 2)</td>
<td>C = 0</td>
<td>100% (1/1)</td>
<td>66.7% (2/3)</td>
</tr>
<tr>
<td>Zafirlukast: Design 'b3' (n = 2)</td>
<td>28-55 yrs (n = 1)</td>
<td>C = 0</td>
<td>0%</td>
<td>44.4% (n = 1)</td>
</tr>
<tr>
<td>Both drugs: All designs (n = 22)</td>
<td>34.2 yrs (n = 5); 6-85 yrs (n = 13)</td>
<td>C = 4.5% (1/22)<em>; A = 18.2% (4/22)</em></td>
<td>63.6% (14/22)</td>
<td>48.9% (n = 10)</td>
</tr>
</tbody>
</table>

**KEY:**

- n = sample size; yrs = years; NR = not reported
- *excludes Johnson, et al, 1999⁷
- **two entries are due to discrepancy in Hughes et al, 1999 report⁸
- **H’s refer only to LTRA vs. IC contrasts of interest to the present review, and with regard to the intention-to-treat principle;
- Children = ages six to 11 years; Adolescents = 12 to 17 years
- Design = LTRA vs. IC in symptomatic pts; Design = LTRA as add-on to IC vs. IC alone in symptomatic pts; Design = LTRA as add-on to IC vs. increasing IC in symptomatic pts; Design = LTRA as add-on to IC vs. IC alone in well-controlled pts, with tapering of IC as primary objective (yet where minimal effective IC dose was sought prior to randomization);
### TABLE 3: Summary of Reported Intervention and Control Intervention Characteristics

<table>
<thead>
<tr>
<th>LTRA Intervention:</th>
<th>IC Intervention:</th>
<th>Mean Intervention Length; Range (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose/schedule (mode)</td>
<td>Dose/Schedule (mode)</td>
<td></td>
</tr>
<tr>
<td>Montelukast: All designs (n = 8 trials)</td>
<td>10 mg od** (n = 7)</td>
<td>BCM 200 ug bid (n = 5)</td>
</tr>
<tr>
<td>Montelukast: Design 'a' (n = 6)</td>
<td>10 mg od (n = 5)</td>
<td>BCM 200 ug bid (n = 3)</td>
</tr>
<tr>
<td>Montelukast: Design 'b1' (n = 1)</td>
<td>10 mg od (n = 1)</td>
<td>BCM 200 ug bid (n = 1)</td>
</tr>
<tr>
<td>Montelukast: Design 'b2' (n = 0)</td>
<td>10 mg hs (n = 1)</td>
<td>ICs (undefined) 300-3,000 ug/day (n = 1)</td>
</tr>
<tr>
<td>Montelukast: Design 'b3' (n = 1)</td>
<td>20 mg bid* (n = 12)</td>
<td>FLU 88 ug bid* (n = 5)</td>
</tr>
<tr>
<td>Zafirlukast: All designs* (n = 14)</td>
<td>20 mg bid* (n = 8)</td>
<td>FLU 88 ug bid* (n = 5)</td>
</tr>
<tr>
<td>Zafirlukast: Design 'a*' (n = 8)</td>
<td>80 mg bid (n = 1)</td>
<td>IC 1,000-4,000 ug/day of BCM, BUD or FLU (n = 1)</td>
</tr>
<tr>
<td>Zafirlukast: Design 'b1' (n = 1)</td>
<td>20 mg bid &amp; 80 mg bid (n = 3)</td>
<td>ICs (undefined) 800-1,000 ug/day; BCM 672 ug/day; BCM 800-1,000 ug/day (each n = 1)**</td>
</tr>
<tr>
<td>Zafirlukast: Design 'b2' (n = 2)</td>
<td>20 mg bid (n = 2)</td>
<td>ICs (undefined); BCM 1,500 ug/day (each n = 1)**</td>
</tr>
<tr>
<td>Zafirlukast: Design 'b3' (n = 2)</td>
<td>All drugs, all designs:</td>
<td>11.7 wks*; 4-39 wks* (n = 22)</td>
</tr>
</tbody>
</table>

Key:

LTRA = leukotriene receptor antagonist;  
IC = inhaled corticosteroid; BCM = beclomethasone, an inhaled IC; FLU = fluticasone, an inhaled IC;  
BUD = budesonide, an inhaled IC  
*excludes Johnson, et al, 1999?  
**5 mg chewable hs for one trial of children ages six to 11 years; od = once daily;  
***three IC interventions, each with one use: ICs (undefined) 800-1,000 ug/day; BCM 672 ug/day; BCM 800-1,000 ug/day  
****two IC interventions, each with one use: ICs (undefined); BCM 1,500 ug/day  
bid = twice daily; hs = at bedtime; wks = weeks;  
Design*a = LTRA vs. IC in symptomatic pts; Design*b = LTRA as add-on to IC vs. IC alone in symptomatic pts; Design*b2 = LTRA as add-on to IC vs. increasing IC in symptomatic pts; Design*b3 = LTRA as add-on to IC vs. IC alone in well-controlled pts, with tapering of IC as primary objective (yet where minimal effective IC dose was sought prior to randomization);
TABLE 4: Summary of Trial Report Quality Ratings, Publication Status and Funding Source

<table>
<thead>
<tr>
<th></th>
<th>Total Quality Score: Mean</th>
<th>Allocation Concealment Score: Mode</th>
<th>% trials published as journal articles</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Montelukast:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All designs</td>
<td>3.5</td>
<td>UNC (n = 8)</td>
<td>62.5% * (n = 5/8)</td>
<td>Merck: 100% (n = 8)</td>
</tr>
<tr>
<td>Design ‘a’</td>
<td>3</td>
<td>UNC (n = 6)</td>
<td>50.0% (n = 3/6)</td>
<td></td>
</tr>
<tr>
<td>Design ‘b1’</td>
<td>5</td>
<td>UNC (n = 1)</td>
<td>100% (n = 1)</td>
<td></td>
</tr>
<tr>
<td>Design ‘b2’</td>
<td>(n = 0)</td>
<td>(n = 0)</td>
<td>(n = 0)</td>
<td></td>
</tr>
<tr>
<td>Design ‘b3’</td>
<td>5</td>
<td>UNC (n = 1)</td>
<td>100% (n = 1)</td>
<td></td>
</tr>
<tr>
<td><strong>Zafirlukast:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All designs</td>
<td>2.5* (n = 14)</td>
<td>UNC* (n = 14)</td>
<td>21.4% (3/14)</td>
<td>GW: 35.7%* (n = 14)</td>
</tr>
<tr>
<td>Design ‘a’</td>
<td>2.2* (n = 8)</td>
<td>UNC* (n = 8)</td>
<td>25% (2/8)</td>
<td></td>
</tr>
<tr>
<td>Design ‘b1’</td>
<td>1</td>
<td>UNC (n = 1)</td>
<td>(n = 0)</td>
<td></td>
</tr>
<tr>
<td>Design ‘b2’</td>
<td>2.7 (n = 3)</td>
<td>UNC (n = 3)</td>
<td>(n = 0)</td>
<td></td>
</tr>
<tr>
<td>Design ‘b3’</td>
<td>3.5 (n = 2)</td>
<td>UNC (n = 2)</td>
<td>(n = 0)</td>
<td></td>
</tr>
<tr>
<td><strong>All drugs:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All designs</td>
<td>2.9* (n = 22)</td>
<td>UNC* (n = 22)</td>
<td>36.4% * (n = 8/22)</td>
<td></td>
</tr>
</tbody>
</table>

**Key:**

UNC: Unclear allocation concealment
* note that 2 reports came from one journal publication: i.e. Laviolette, et al, 19992
*Johnson, et al, 199977
Merck = Merck Frosst; GW = Glaxo Wellcome; AZ = Astra Zeneca

Designa = LTRA vs. IC in symptomatic pts; Designb1 = LTRA as add-on to IC vs. IC alone in symptomatic pts;
Designb2 = LTRA as add-on to IC vs. increasing IC in symptomatic pts;
Designb3 = LTRA as add-on to IC vs. IC alone in well-controlled pts, with tapering of IC as primary objective (yet where minimal effective IC dose was sought prior to randomization).
APPENDIX A: METHODS INFORMATION

Study Identification

Using search strategies designed for particular databases (Appendix B for a validated Medline strategy), a number of electronic sources were consulted: Medline (1966 to December 1999), Embase (1988 to June 1999), Pre-Medline (180 days, ending July 22, 1999), Biological Abstracts (1993 to September 1999), CINAHL (1982 to April 1999), and Dissertation Abstracts (1990 to May 1999). After evaluating the results of all of these searches, the decision was made to limit updating to Medline.

To illustrate, relative to an initial Medline search (1966 to June 1999), of the 34 citations unique to an initial search of Embase (1988 to June 1999), none were deemed by way of broad screening assessment to refer to trials potentially relevant for the present review (section 2.4 and Appendix A: The Selection Process). Likewise, the other databases produced no added value beyond Medline’s yield. Thus, the strategy employed for updating entailed the periodic re-running of the Medline search strategy, restricting the results to material added since the previous update. The final Medline search update covered the period ending December, Week 2, 2000.

The Cochrane Library’s Controlled Clinical Trials Registry was consulted (2000, Issue 3) and this constituted a surrogate hand search. Trial registries (e.g. Current Controlled Trials) were consulted for unpublished or ongoing trial information and data. Searches were not restricted by language of publication, year of publication, or publication status (e.g. grey literature). An additional search was conducted in Medline (1966 to June 1999) using the subject terms (section A2.2 below) and a filter designed to detect systematic reviews. The Cochrane Library (2000, Issue 3) was also consulted to identify systematic reviews.

The reference lists from textbooks, systematic or narrative reviews and reports of trials included in the present review were examined in an effort to identify additional trial material. Recently published issues of journals recommended by the content experts were searched manually for abstracts and, in particular, for supplement issues containing pertinent conference proceedings. These included, but were not restricted to: American Journal of Respiratory and Critical Care Medicine (1995 through 1999, inclusive), Chest (1995 through 1999, inclusive), and Journal of Allergy and Clinical Immunology (1995 through 1999, inclusive). The libraries of content experts other than those devoted to the present project were consulted. The manufacturers of the LTRAs investigated herein were approached for additional trial reports as well as to clarify or supplement information and data contained in identified abstracts or conference proceedings (e.g. posters) (section 2.6).

Search Terms

The subject terms for the present searches of bibliographic databases were: asthma, wheezing, respiratory sounds, leukotrienes, leukotriene antagonists, zafirlukast, montelukast, Beclomethasone, Triamcinolone acetonide, Budesonide, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, inhaled corticosteroid, and inhaled glucocorticosteroid (Appendix B). The searches used subject headings tailored to each source as well as free text
terms in the titles and abstracts. Where appropriate, a method-centred filter was added to capture randomized controlled trials (RCTs) (Appendix B). This latter approach was not employed when a database (e.g. Current Controlled Trials) consisted mostly of RCTs, or where the search interface did not permit complex searching. The overarching goal in bibliographic searches was to maintain a high level of sensitivity.

The Selection Process

To begin with, two individuals independently screened the title, abstract and key words for each citation by liberally applying the inclusion criteria to determine whether or not to retain it. A citation was retained if its title, abstract or key words suggested it might contain information or data elucidating the efficacy and/or safety of montelukast or zafirlukast relative to that of ICs. Where there was a divergence of opinion concerning a citation’s possible relevance, or there was just one broad screener who was at best uncertain as to its relevance, it was entered into the next phase of the review. The reasons for the ineligibility of studies were noted (Figure 1 and section 3.3 and Appendix F).

Citations identified from these searches were entered into a Reference Manager database and duplicates were removed manually. The retained citations comprised the ‘potentially relevant’ documents. Hard copies of all potentially relevant documents were retrieved.

To reduce bias, oversight and inconsistency, two reviewers then independently reviewed each document to formally determine eligibility using a Relevance Form (Appendix C). The form comprised questions related to the inclusion criteria, and the questions addressed issues of study design, population, intervention and outcomes. An affirmative answer to each of these questions deemed that the article had passed the ‘relevance filter’ and it was then included in the systematic review.

All disagreements were resolved by consensus while impasses were settled by a third person. The reasons for excluding studies were noted (Figure 1). Qualitative reports (e.g. reviews, case reports, letters, opinion papers, editorials) were retained for future use and their reference lists were checked for possible trials.

A two-rater calibration exercise as well as an inter-observer reliability study preceded the evaluation of the complete set of potentially relevant materials. The rate of agreement involving 23 randomly selected, potentially eligible reports entered into relevance assessment (e.g. full-text reports; abstracts) was 100%. All remaining reports of varying publication status (e.g. published papers; conference abstracts) were independently evaluated by these assessors. At no time in this review was a third party required to break an impasse when it came to independent evaluations of information or data.

Data Abstraction

To ensure quality control, three reviewers were employed to extract and document the data from each included trial. After a training session, each reviewer abstracted different types of data while checking each other’s work against the original reports. The original reports were not masked as there is conflicting evidence regarding the benefit of this practice.35

Individualized data abstraction forms reflecting each of the four research questions or designs (i.e. ‘a’ through ‘b3’), had been developed a priori in consultation with the content experts. They
provided an opportunity to capture information or data concerning: report characteristics (e.g. publication status); study characteristics (e.g. design; number of centres); population characteristics (e.g. clinical parameters defining asthma); intervention characteristics (e.g. dose/schedule of LTRAs); control intervention characteristics (e.g. dose/schedule of ICs); efficacy outcomes (e.g. pulmonary function); and adverse event outcomes (e.g. elevated liver enzymes).

For each question or design the content experts established a consensus on the most clinically relevant, primary efficacy outcomes. For design ‘a,’ no type of efficacy outcome was considered more or less clinically significant, and so, all were deemed potentially pertinent (e.g. pulmonary function tests (FEV₁, PEF); responses to asthma exacerbations (e.g. beta₂-agonist rescues; systemic steroid rescues); asthma exacerbations (e.g. number, severity, duration of episodes); functional status; day and/or nighttime symptom scores; indexes of airway inflammation (e.g. levels of seroeosinophil); quality of life, etc.). For each of designs ‘b1’ and ‘b2,’ the primary outcome was the ‘number of exacerbations requiring systemic corticosteroid use.’ This outcome was chosen because exacerbations have a large potential impact on asthma costs due to health care utilization and time missed from work or school. They can also lead to asthma mortality. Finally, the ‘b3’ design employed the following primary outcomes: percent change from baseline in required maintenance dose of ICs’ and/or ‘the final IC dose’. Adverse event outcomes of a short or long term nature included, but were not limited to, eosinophilic vasculitis and elevated liver enzymes.
### APPENDIX B: MEDLINE SEARCH STRATEGY

Medline search strategy for randomized controlled trials involving leukotriene receptor antagonists compared to inhaled corticosteroids

<table>
<thead>
<tr>
<th>Set</th>
<th>Search</th>
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<tr>
<td>001</td>
<td>exp asthma</td>
</tr>
<tr>
<td>002</td>
<td>asthma$.tw.</td>
</tr>
<tr>
<td>003</td>
<td>wheez$.tw.</td>
</tr>
<tr>
<td>004</td>
<td>respiratory sound$.tw.</td>
</tr>
<tr>
<td>005</td>
<td>(clinical trial or controlled clinical trial).pt.</td>
</tr>
<tr>
<td>006</td>
<td>randomized controlled trial.pt.</td>
</tr>
<tr>
<td>007</td>
<td>(random$ or placebo$).tw.</td>
</tr>
<tr>
<td>008</td>
<td>double-blind$.tw,sh.</td>
</tr>
<tr>
<td>009</td>
<td>single-blind$.tw,sh.</td>
</tr>
<tr>
<td>010</td>
<td>exp leukotrienels/</td>
</tr>
<tr>
<td>011</td>
<td>exp leukotriene antagonists</td>
</tr>
<tr>
<td>012</td>
<td>leukotriene$.tw.</td>
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<td>zafirlukast.tw.</td>
</tr>
<tr>
<td>014</td>
<td>montelukast.tw.</td>
</tr>
<tr>
<td>015</td>
<td>Beclomethasone/or Triamcinolone acetonide</td>
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<td>Budesonide</td>
</tr>
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</tr>
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<td>(inhal$ adj3 corticosteroid$).tw.</td>
</tr>
<tr>
<td>023</td>
<td>(inhal$ adj3 glucocortic$).tw.</td>
</tr>
<tr>
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<td>or/1-4</td>
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<td>or/5-9</td>
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<td>or/10-14</td>
</tr>
<tr>
<td>027</td>
<td>or/15-23</td>
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<tr>
<td>028</td>
<td>and/24-27</td>
</tr>
</tbody>
</table>
APPENDIX C: RELEVANCE ASSESSMENT FORM

LTRA SYSTEMATIC REVIEW (01/00)

REVIEWER: ___________________ REFERENCE ID# ____________

Please respond to each question.

1. Did the study include any of the following research foci (circle one or more): _____ YES _____ NO
   a. an inhaled corticosteroid (IC) vs. leukotriene receptor antagonist (LTRA), or
   b. the additive effects of an LTRA in patients on IC(s):
      b.1. in patients on IC(s), adding LTRA(s) vs. placebo (i.e. maintaining the original IC dose), or
      b.2. in patients on IC(s), adding LTRA(s) vs. increasing the IC(s) dose, or
      b.3. in patients on IC(s), adding LTRA(s) to reduce the IC(s) dose vs. placebo (i.e. maintaining the original IC dose)*

   * only RCTs in which the minimal effective dose of IC was sought prior to randomization will be considered

2. Did all members of this population receive a diagnosis of ‘asthma’ using a systematic and reproducible method and system of diagnostic criteria? _____ YES _____ NO

3. Did the study include any of the following home, lab or office-assessed outcomes? _____ YES _____ NO

   (circle one or more):
   a. pulmonary function (e.g. FEV1, AM Peak expiratory flow value, PM peak expiratory flow value), or
   b. indexes of airway inflammation (e.g. levels of: seroeosinophils, sputum eosinophils, eosinophil cationic protein, exhaled nitric oxide, basophils?, cytokines?), or
   c. [rate(s) of] type of exacerbation, morbidity or mortality, or
   d. (rates of) response(s) to exacerbations (e.g. (changes in) systemic steroid rescue; beta2 agonist rescue; IC dose; hospitalizations; emergency room visits; other unscheduled physician visits), or
   e. daytime or nighttime symptom rate(s) and score(s) (e.g. nocturnal asthma episodes), or
   f. quality of life, or
g. short- or long-term adverse events (e.g. suppressed hypothalamic-pituitary-adrenal axis function; decreased bone mineral density, osteoporosis or fractures; growth suppression; glaucoma; cataracts; gastrointestinal discomfort; elevated liver enzymes (serum alanine aminotransferase); Churg-Strauss eosinophilic vasculitis syndrome; other hypereosinophil syndromes), or

h. long-term events (e.g. alterations in natural history of the disease; ‘remodeling’ of sub-basement membrane thickness).

4. Were members of the population randomly assigned to their treatment condition?  _____ YES  ____ NO

5. Did the intervention last at least four weeks?  _____ YES  ____ NO

6. Should this study be included in the systematic review?  _____ YES  ____ NO

(YES only if YES to each of the previous questions)

6.1. If there was a lack of inter-reviewer agreement in response to Q. 6, what is the final consensus decision?  _____ YES  ____ NO

6.2. The basis for this consensus decision is:
APPENDIX D: TRIAL QUALITY ASSESSMENT FORM

TRIAL REPORT QUALITY

1. Randomization: Was the study described as randomized (i.e. including words such as randomly, random, randomization)?

   Yes = 1   No = 0

A trial reporting that it is ‘randomized’ is to receive one point. Trials describing an appropriate method of randomization (table of random numbers, computer generated) receive an additional point.

   Appropriate = 1   Not appropriate = 0

However, if the report describes the trial as randomized and uses an inappropriate method of randomization (e.g. date of birth, hospital numbers), a point is deducted.

   TOTAL POINTS: 0   1   2

   SCORE = _________

2. Double-blinding: Was the study described as double-blind?

   Yes = 1   No = 0

A trial reporting that it is ‘double-blind’ is to receive one point. Trials that describe an appropriate method of double-blinding (identical placebo: colour, shape, taste) are to receive an additional point.

   Yes = 1   No = 0

However, if the report describes the trial as double-blind and uses an inappropriate method (e.g. comparison of tablets vs. injection with no dummy), a point is deducted.

   TOTAL POINTS: 0   1   2

   SCORE = _________

3. Withdrawals and dropouts: Was there a description of withdrawals and dropouts?

   Yes = 1   No = 0

A trial reporting the number of and reasons for withdrawals or dropouts is to receive one point. If there is no description, no point is given.

   OVERALL SCORE: _________

   Low = 0-2 points
   Moderate = 3-4 points
   High = 5 points (max.)

4. Adequacy of Allocation Concealment: (circle one):

   ~ Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes, etc ............................................................. = ADEQUATE

   ~ Alternation; reference to case record # or date of birth, etc. = INADEQUATE

   ~ Allocation concealment is not reported or fits neither category = UNCLEAR
APPENDIX E: The Decision to Forego Meta-analysis

Concerning all ‘a’ design studies (i.e. published or unpublished), a number of difficulties were observed and which precluded serious consideration of a quantitative synthesis. Looking first at montelukast, for each one of the 18 different primary outcomes employed across the eight RCTs, there appeared to be at least two potentially poolable instances of trial data. However, of these 18 primary outcomes, 12 could be readily identified as having data-related problems. These are described in Figure 2 (section F2.1: items 1 through 12, inclusive).

For example, a significant part of the problem identified in item 12 (Figure 2) was that extractable data would have to come from unverified grey literature reports. As expressed earlier, such documents can be limited in their ability to fully and faithfully represent an RCT’s methods and findings; and, without feedback from the pharmaceutical companies, there could be no way to ascertain the validity of their reported results. Consequently, it was decided that the grey literature material could not be submitted to a quantitative synthesis. For the same reason, two other instances of primary outcome data were excluded from pooling (Figure 2, section F2.1: items 13 and 14). This left four primary outcomes with potentially poolable data.

The same two published trials provided data for each of the following outcomes: serum eosinophils (change from baseline); compliance monitored by pill counts (%) or by canister weight (%); and dropouts and active withdrawals (%). However, it was assumed that in no way could the efficacy of LTRAs relative to that of ICs be expressed in the most clinically relevant terms using any of these four outcomes. Not one is a direct index of a patient’s experience of the impact of the intervention on their asthma.

Indexes of pulmonary function (e.g. AM PEF) or exacerbations requiring (e.g. systemic corticosteroid) rescue would likely be better candidates for primary outcomes in ‘a’ designs. As a result, without poolable data from clinically significant outcomes, it was decided not to quantitatively evaluate any of the four, less revelatory outcomes having only two trials worth of data each. The lack of poolable data for clinically significant outcomes also helped resolve any concerns that the present review had erred in failing to specify, a priori, a limited number of the most clinically relevant, primary outcomes for ‘a’ designs in a way paralleling the discernments made for each of the other three research foci (i.e. ‘b1’ through ‘b3’).

Focusing on zafirlukast-related ‘a’ design studies, it was observed that there were several outcomes with potentially combinable data (e.g. FEV$_1$: change from baseline) in the two published studies. However, without clarification of the possible overlap of one of them with two reports already included, a quantitative synthesis could not be considered appropriate. Also, for each of four different primary outcomes across the remaining zafirlukast RCTs, there appeared to be potentially poolable data from at least two trials. However, these studies were described by grey literature reports. Other data-related impediments to pooling data from the zafirlukast-centred RCTs are delineated in Figure 2 (section F2.2). In large part because of the unverified status of their reports, data from zafirlukast reports could not be synthesized quantitatively. Seen together, these montelukast- and zafirlukast-related observations quashed any possibility of pooling data for ‘a’ design studies across the two LTRA drugs.
Still on the subject of primary outcomes, attention is now turned to the other three research foci addressed in this review. For each of the ‘b1’ and ‘b2’ trial designs, and for each of the two LTRAs, only the Virchow, et al,’71-73,80’ zafirlukast, ‘b1’ design study reported data pertaining to the primary outcome. On the other hand, one ‘b3’ design document actually contained published montelukast results for each of two clinically relevant primary outcomes (i.e. required maintenance dose of ICs (percent change from baseline); and final maintenance dose of ICs). However, in that no other montelukast-centred ‘b3’ design RCTs were identified by this review, pooling became impossible.

Regarding zafirlukast, there were two different, unverified grey literature documents, each of which reported having employed primary outcomes with a ‘b3,’ IC-tapering focus. However, for one of the primary outcomes, neither report presented zafirlukast-related data (i.e. required maintenance dose of ICs (change from baseline)). The reports associated with the other ‘b3’ primary outcome (i.e. required maintenance dose of ICs (percent change from baseline)) were unverified pieces of grey literature. For the single ‘b3’ primary outcome (i.e. required maintenance dose of ICs (percent change from baseline)) having three potential contributions in total from the two LTRAs combined, two of the trial reports were unverified instances of grey literature. Thus, pooling was not possible for ‘b3’ design data. Finally, of the eight included RCTs with an LTRA-related research focus other than an ‘a’ design, only four described having used what this review’s content experts had defined as the clinically relevant, primary outcomes.

Outcomes regarded as secondary were not considered by the content experts to be clinically significant pieces of evidence with which to express the efficacy of LTRAs relative to ICs. On this basis, as well as following the observation that much of the secondary outcome data was limited or problematic (e.g. unverified grey literature documents), no syntheses of secondary outcome results were considered with respect to research foci ‘b1’ through ‘b3.’

Sparse adverse event data were observed in both zafirlukast- and montelukast-centred study reports. For example, three types of montelukast-related adverse event were readily excluded from consideration on the basis of limited or problematic data (Figure 2, section F2.3: items 1 through 3, inclusive). All were observed in ‘a’ design study reports.

On the other hand, there were six adverse event outcomes for which there were potentially poolable data. Each outcome was extractable from the same two published montelukast RCTs (% of patients with: headache; upper respiratory tract infection; influenza; pharyngitis; patients with worsening asthma; and death). However, without even a provisional picture of LTRAs’ relative efficacy expressed by verified and clinically significant, outcome data, it was decided not to analyze these data. Safety results alone cannot be used to evince LTRAs’ relative utility. That is, without an evidence-based definition of the degree of efficacy, one cannot derive a clinically pertinent, cost-benefit picture of utility.
APPENDIX F: REPORT CHARACTERISTIC RESULTS

Of the 185 reports entered into the broad screening process, 125 were excluded. Reasons for exclusion are provided in Figure 1. The remaining 60 reports were identified as being potentially relevant, and all but one were retrieved and then assessed formally for relevance. Another 17 reports were then excluded, and for the reasons provided in Figure 1.

One of the remaining 43 included reports was an abstract which had to be excluded from the review. The reviewers had determined that the trial described in this report was virtually indistinguishable from the one detailed by two other reports and thus their relationship required some clarification from the pharmaceutical company. However, without any feedback from the pharmaceutical companies, it was decided to note this report in Table 1 while excluding its details from any qualitative assessments (Tables 2 through 4). Technically speaking, this eliminated it from the present review. The decision was made to prevent the possible entry of duplicate information into qualitative summaries (Tables 2 through 4).

Within the remaining set of trial reports, each of two documents reported methods and data satisfying the same two types of design (i.e. ‘a’ and ‘b1’). One document was an abstract that was eventually published as a paper. Thus, each had to be submitted twice for formal relevance assessment.

Reports were retrieved exclusively from English-language sources (e.g. journals, conference proceedings). However, of the 22 unique trials, only 36.4% (8/22) had information or data drawn from a journal-published document. This percentage is inflated somewhat given that one published report contributed data from two trial designs.

When information or data were summarized (Tables 2 through 4), the policy was that journal-published information or data should take precedence over the details contained in grey literature. Finally, data from the most recent and/or more all-encompassing reports were included in summaries of trials.
APPENDIX G: POPULATION CHARACTERISTIC RESULTS

For montelukast trials (n = 8), in total there were 3,396/3,397 trial participants (Table 2). The mean sample size was 424.5/424.6 individuals, with a range from 12 to 1,282 participants. For zafirlukast (n = 11) trials, the total and mean sample sizes were 3,574 and 324.9 participants, respectively. The sample sizes ranged from nine to 481 individuals. Thus, montelukast trials were fewer in number yet included, on average, more participants. Each drug was associated with one very small trial,\textsuperscript{51,79} and all three trials missing sample size information were grey literature reports of zafirlukast studies.\textsuperscript{65, 67-69, 74}

There was a paucity of whole sample age information for both montelukast and zafirlukast studies (Table 2). The age range of participants for montelukast trials (six to 85 years) was wider than for zafirlukast studies (12 to 69 years). However, at times it was not possible to discern whether these age ranges had been trial selection criteria or descriptions of the individuals randomized to treatment.

Very few trials provided information sufficiently specific to permit the discernment that a trial had focused exclusively on children (i.e. ages six to 11 years) (4.5%: 1/22) or on adolescents (i.e. ages 12 to 17 years) (4.5%: 1/22) (Tables 1 and 2). The studies involved montelukast\textsuperscript{51} and zafirlukast,\textsuperscript{70} respectively. Furthermore, 63.6% (14/22) of trial reports supplied details sufficiently specific to allow the determination that some adolescents had likely been included in a sample trial (Tables 1 and 2). At times it was not possible, however, to discern whether these reported age ranges constituted trial selection criteria or descriptions of the individuals randomized to treatment. Three quarters of montelukast trials (6/8) and 57.1% of zafirlukast studies (8/14) contained enough information to afford the observation that some adolescents had likely been selected. However, in no trial report of a study likely including some adolescents was there a specific breakdown of information or data by age or developmental stage (e.g. adolescents vs. adults).

The median ‘percent male’ composition for all included trials was 48.9% (Table 2). However, only 10 studies reported information affording this calculation. Few zafirlukast reports provided gender breakdown information. Sample size, age and ‘percent male’ figures broken down by research focus (i.e. design) are provided in Table 2.
APPENDIX H: INTERVENTION AND CONTROL INTERVENTION CHARACTERISTICS RESULTS

Given the different drugs and their divergent dose magnitudes and schedules, the following results are presented separately for the two LTRA interventions. Dose values reflect U.S. dose labeling. For montelukast, in seven of eight trials, the LTRA intervention was 10 mg once a day (od) (Table 3). The only other LTRA intervention involved a five mg chewable tablet given to children once a day at bedtime. For zafirlukast, 20 mg bid was investigated in 12 of 14 trials. Other zafirlukast interventions included 40 mg twice a day (bid) or 80 mg bid used instead of, or to compare with, the typical 20 mg bid dose (Table 1).

The IC interventions employed as control interventions for LTRAs varied (Tables 1 and 3). In five of eight montelukast studies, the control intervention was beclomethasone 200 ug bid. Four of these trials involved an ‘a’ design. Other control interventions included: fluticasone 88 ug bid vs. budesonide 200 ug bid; Beclomethasone 100 ug three times a day (tid) in a study of children; and, ICs (undefined) 300-3,000 ug per day.

When combined with montelukast in the ‘b1’ design, the IC intervention to which montelukast was added was BCM 200 ug bid. ICs (undefined) 300-3,000 ug/day were supplemented with montelukast in the ‘b3’ design.

In zafirlukast trials (n = 14), the most frequently employed control intervention was fluticasone 88 ug bid (n = 5) (Tables 1 and 3). Other control drugs were represented, including various doses of beclomethasone (i.e. 100-200 ug bid; 200-250 ug bid; 672 ug/day; 800-1,000 ug/day; 1,500 ug/day). On three occasions, IC control doses were not specified in the trial reports: ICs 1,000-4,000 ug/day of beclomethasone, budesonide or fluticasone. When combined with zafirlukast in a ‘b1’ design, the IC intervention included: ICs 1,000-4,000 ug/day of beclomethasone, budesonide or fluticasone. ICs (undefined) 800-2,000 ug/day; and ICs (undefined).

When combined with zafirlukast in a ‘b2’ design, the IC interventions included: ICs (undefined) 400-500 ug/day; and beclomethasone 336 ug/day. When combined with zafirlukast in a ‘b3’ design, the IC interventions included: ICs (undefined) 800-2,000 ug/day; and beclomethasone 1,500 ug/day. Intervention length, modal LTRA intervention and modal control intervention data are broken down by research focus (i.e. design) in Table 3.
Irrespective of the primary LTRA intervention, 63.6% (14/22) of the included trials satisfied the relaxed requirements (i.e. a priori or ad hoc definitions of ‘mild-to-moderate, chronic or recurrent asthma’) for an ‘a’ design, while two and three studies met the similarly relaxed criteria for ‘b1’ and ‘b2’ designs, respectively (Table 2: Column 1). Three trials were considered appropriate instances of a ‘b3’ design. Three quarters of montelukast trials and 57.1% (8/14) of zafirlukast studies entailed ‘a’ designs, making the latter drug more likely to have investigated the ‘LTRA as add-on’ type of research question.

Twenty of 22 trials (90.9%) employed parallel designs (Table 1). Two were of the crossover variety. Of the 20 parallel trials, two took the form of randomized extensions to other trials (Table 1).
APPENDIX J: TRIAL REPORT QUALITY RESULTS

Where there were discrepancies in ratings of trial quality obtained for multiple reports referring to the same trial, the highest rating was used. For example, a rating of ‘4’ was entered into summaries of an overarching trial described by five reports.52-56

Trial report quality data revealed that in none of the trial reports could it be determined unequivocally that treatment allocation had been concealed (Tables 1 and 4). Thus, the allocation concealment results did not vary either as a function of the publication status of reports or the trials’ research focus (i.e. design).

The modal total quality score for all included studies was one (31.8%: 7/22 trials), with scores ranging between one (Low quality) and five (High Quality). For five of 22 trials (22.7%), the composite trial report quality was determined to be five, indicating high quality. The mean quality value for all 22 trials was 2.9, and the average montelukast rating (3.5; n = 8) exceeded that for zafirlukast trials (2.5; n = 14) (Table 4).

For 10 trials (45.5%: 10/22) the maximum score for double-blinding (i.e. two) was assigned while for six trials (36.4%: 8/22) the maximum rating for randomization (i.e. two) was given (Table 1). Regarding randomization, 5 and 3 were montelukast and zafirlukast studies, respectively. When it came to double-blinding, 5 and 5 had been montelukast and zafirlukast trials, respectively. In nine trial reports (40.9%: 9/22) withdrawals and dropouts were described. Of these, 4 and 5 were montelukast and zafirlukast studies, respectively.