Asthma Pharmacotherapy Adherence Interventions for Adult African-Americans: A Systematic Review

By

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Abstract:

Background: Adult African American (AA) asthmatics have high rates of nonadherence to pharmacotherapy; however little is known about interventions to improve adherence in this population.

Purpose: To systematically review the literature on patient and family-level interventions aimed at improving pharmacotherapy adherence in adult AA asthmatics.

Data Sources: MEDLINE®, EMBASE, Web of Science, and CINAHL from inception to February 2016; reference lists of key studies on this topic.

Study Selection: English-language studies enrolling adult AA asthmatics from the US comparing patient and/or family-level interventions to improve asthma pharmacotherapy with usual care, no intervention or another active intervention.

Data Extraction: Two investigators independently selected, extracted data from and rated the risk of bias of relevant studies.

Data Synthesis: 1,460 unique abstracts were identified from all sources, 3 randomized controlled trials (RCT) and 1 pre/post study met inclusion criteria. Studies ranged from 17-333 participants who were predominately middle-aged (33-47 years), AA (71%-93%), and women (69%-82%). The 3 RCTs enrolled patients with persistent asthma and evaluated three different types of interventions: problem solving, self-efficacy, and the use of patient advocates. All 3 compared the intervention with an active control featuring minimal asthma education, and we rated all three as having a medium risk of
bias. None of the RCTs found a statistically significant improvement in adherence, FEV1, asthma control, asthma self-efficacy, or health care utilization outcomes. The RCT assessing self-efficacy (N=42) found a clinical and statistically significant improvement in asthma quality of life (adjusted difference between groups: 1.8, p=0.002). The pre/post study (N=17) evaluated a pharmacist-led educational intervention enrolling hospitalized asthmatics; we rated this study as having a high risk of bias primarily due to selection bias. Compared with baseline, participants had improved adherence at 6 months (absolute increase adherence rate 41%, p=0.0175) and reduced asthma-related ED and hospital visits (absolute reduction 1.23 visits per person, p=0.0016).

Limitations: Small, diverse body of literature with some methodological limitations such as attrition, selection bias and measurement bias; possible publication bias

Conclusion: Few studies assessing asthma adherence interventions focused on adult AA populations. Limited data from one RCT suggests that interventions focused on self-efficacy improve asthma related quality of life compared with controls. Although one pre/post study found improved adherence with a pharmacist-led intervention, none of the 3 included RCTs demonstrated improved adherence in participants randomized to an active intervention compared with controls.
Introduction

Asthma is a chronic inflammatory disorder of the airways that is characterized by variable and recurring symptoms, airflow obstruction and bronchial hyper-responsiveness.\textsuperscript{1,2} Evidence suggests that most patients with asthma can control their disease if they receive guideline-based care, use appropriate asthma pharmacotherapy, and modify their environment to reduce or eliminate exposure to allergens and irritants.\textsuperscript{2-7} However, adult African Americans are disproportionately burdened by asthma. African Americans are 20% more likely to have asthma compared with Non-Hispanic whites (current asthma prevalence of 8.6\% vs 7.3\%); but, more than three times more likely to have a hospitalization (rate per 100,000 population, 297.9 vs 90.5) or death due to asthma (rate per 100,000 population, 2.6 vs 0.8) compared with Non-Hispanic whites.\textsuperscript{8-10} While African American children with asthma have higher health care utilization rates, adult African American asthmatics have higher mortality rates.\textsuperscript{11}

Adherence to asthma pharmacotherapy is integral to preventing asthma exacerbations and can help reduce asthma disparities.\textsuperscript{12} Medication adherence is defined as the extent to which patients take medications as prescribed by their health care providers.\textsuperscript{13} Nonadherence to asthma therapy is associated with poor asthma health outcomes (e.g., asthma exacerbations, asthma quality of life, asthma control), increased health care utilization (e.g., emergency department visits, outpatient visits, hospitalizations) and asthma-related mortality.\textsuperscript{14,15} It is estimated that about 25\% of asthma exacerbations in African Americans can be prevented by inhaled corticosteroid (ICS) adherence.\textsuperscript{12}
Barriers to adherence occur at all levels of the socio-ecological framework and range from patient-related (e.g., cost, perceived effectiveness, and health beliefs), therapy-related (e.g., complexity of regimen, frequent medication changes, side effect) provider-related (e.g., patient-provider relationship, patient-provider communication), and health-system related (e.g., lack of continuity of care, poor access to appointments, patient information written at high literacy level). Patient characteristics associated with nonadherence include external variables such as minority race/ethnicity, low income, and non-private insurance and internal variables such as decreased readiness to take controller medication and unfavorable attitudes towards controllers.

Le et al., found that negative health beliefs mediated the relationship between minority race/ethnicity and poor adherence. When they controlled for negative health beliefs, the relationship between minority race/ethnicity was no longer significant (unstandardized, Beta = -0.25, p = 0.01 to Beta = -0.17, p=0.08). However Apter et al., did not achieve similar results when adjusting for attitude towards ICS. Attitude was only associated with a 13% reduction in the race coefficient, which was lower than their a priori threshold limit of 15%. Their mediation analysis found that household income, commercial insurance, and symptoms within the prior 2 weeks was associated with a 32%, 42% and 23% reduction in association between race/ethnicity and adherence, respectively.

Prior systematic reviews exploring asthma adherence interventions have noted variable effectiveness in improving adherence and asthma clinical outcomes. A 2003 systematic review of adult and pediatric asthmatics concluded that interventions with improved adherence and asthma control were often education interventions and
used subjective adherence and clinical outcome measures.\textsuperscript{21,25-28} In 2012 Moullec et al., reviewed adherence interventions in adult asthmatics and concluded that interventions with a higher number of chronic care model components (i.e., self-management, decision support, delivery system design, clinical information system) had higher ICS adherence--one component, standardized mean difference 0.29, 95% CI (0.16-0.42); two components 0.53 (0.40-0.66); four components 0.83, (0.69-0.98).\textsuperscript{23} A recent Cochrane Review of medication adherence interventions across all diseases concluded that there were few low risk of bias randomized controlled trials (RCT) that improved adherence and clinical outcomes. They found no common intervention components in effective trials and small effect sizes overall.\textsuperscript{29}

Prior systematic reviews did not assess the effectiveness of adherence interventions in high-risk asthma populations (i.e., inner city, race/ethnic minorities, low income) who have a higher relative risk of nonadherence, a history of increased adverse asthma outcomes, and may respond differently to interventions due to variable health behaviors and beliefs.\textsuperscript{30,31} Consequently, we sought to identify patient and family level interventions that were effective in improving patient adherence to asthma pharmacotherapy in adult African Americans.

### Methods

#### Literature Search Strategy

We searched MEDLINE®, Excerpta Medica database (EMBASE), Web of Science (WOS) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) from inception to January-February 2016. An experienced medical librarian conducted the
searches and we performed quality checks to ensure that we identified known studies on our topic. Our search strategy used a combination of Medical Subject Headings (MeSH) terms and key words focused on “asthma”, “adherence” and “African American”. See Appendix Tables 1-4 for our full search strategy.

We searched WOS to identify unpublished studies and conference abstracts. We also manually searched the references of pertinent reviews, trials and background articles for additional citations that our search may have missed. We determined appropriateness of publications by the same inclusion and exclusion criteria as the original searches (described below). All citations were imported into an EndNote X7 electronic database.

**Inclusion and Exclusion Criteria**

The eligibility criteria were developed with the assistance of an expert panel (Table 1). We included studies enrolling adults (age 18 or older) or studies enrolling adults and children as long as they reported outcomes separately for adults. We were interested in adherence interventions targeting high-risk populations so we limited eligibility to adult African American asthmatics. We excluded studies targeting other (non-African American) race/ethnic groups because prior studies have demonstrated different barriers to adherence in each race/ethnic group (e.g., cultural beliefs, language, immigration status). We required that studies enroll at least 30% African Americans or report subgroup analysis by race. We selected studies with 30% or greater African Americans to be inclusive of studies with diverse race/ethnic composition but to select for studies that had a larger African American populations compared with national percentages.
Interventions had to measure asthma pharmacotherapy adherence for at least one month and target patients or patient family/care-givers. Follow up was at least one month because ICS, first-line therapy for asthma, takes at least four weeks to reach maximal efficacy.\textsuperscript{32-35} We focused on interventions targeting patient and patient-family/caregivers because we wanted to identify interventions that can empower patients and their family/care-givers.

Our primary outcome of interest was adherence. We included any measure of adherence—objective or subjective. Our secondary outcomes of interest, which did not affect eligibility for inclusion, were asthma-related health outcomes, health care utilization and intermediate outcomes. The asthma-related health outcomes included, but were not limited to the following: asthma exacerbation, forced expiratory volume in one second (FEV1), asthma control, asthma quality of life and mortality. Health care utilization outcomes were defined as any asthma-related or any-cause health services use including emergency department, outpatient and hospitalization visits. We limited intermediate outcomes to those related to asthma knowledge and self-management.

Interventions had to be conducted in the United States, or report outcomes separately by site if they were multinational studies. We included trials, cohort studies and single group pre/post studies published in English.

Study Selection

Two members of the team (IR, ZR, BM) independently reviewed all titles and abstracts for eligibility. Full-texts of abstracts or titles that appeared to meet eligibility criteria (or could not be fully assessed) were dually reviewed against the same criteria.
We reviewed the full text of abstracts or titles marked for inclusion by either reviewer. Two team members independently re-reviewed the full text of articles when there was an inclusion/exclusion discrepancy; conflicts were resolved by discussion and consensus.

For conference abstracts, we searched for full text articles and additional reported outcomes in MEDLINE, google scholar, and the clinicaltrials.gov database. We excluded conference abstracts if no associated peer-reviewed publications were identified.

All inclusion and exclusion decisions were tracked in an EndNote database and Microsoft Excel®. We recorded the main reason for exclusion at each stage.

**Data Extraction**

For studies meeting our inclusion criteria, we designed and used structured data extraction forms to gather pertinent information from each article, including study participants, design, setting, interventions, comparators, methods, and results. We extracted relevant data and a second member of the research team reviewed it. All data abstraction was performed using Microsoft Excel® and Word® software.

**Risk-of-Bias Assessment of Individual Studies**

We used the AHRQ Methods Guide to assess the risk of bias (internal validity).36 The criteria included an assessment of selection bias, confounding, performance bias, detection bias, and attrition bias. Appendix Table 5 lists the questions used to assess risk of bias.
A study with “low risk of bias” is considered to have valid results and scored favorably on most questions with relatively minor unfavorable responses (e.g., lack of masking in behavioral interventions). A study with “moderate risk of bias” was concluded to not have major risk of bias but has some risk of bias that will not invalidate its results. However, a study evaluated as “high risk of bias” has errors in design, conduct or analysis that may invalidate its results. Common errors in “high risk of bias” studies can include high rates of attritions, no intention to treat (ITT) analysis, and use of invalid measures of outcomes.

Two independent reviewers assessed the risk of bias for each study. We resolved disagreement by discussion and consensus.

Data Analysis and Synthesis

To determine whether a meta-analysis was appropriate, we assessed the clinical and methodological heterogeneity assessing the PICOTS (population, intervention, comparator, outcome, time, setting) of included studies.

Results

We identified 1,460 unique titles and abstracts and assessed 171 full texts for eligibility (Figure 2). We excluded 168 articles for various reasons (e.g., not conducted in the US, exclusive pediatric population, no intervention, not about asthma) and included 3 randomized controlled trials (RCTs)\(^{37-39}\) and one single arm pre/post study.\(^{40}\) Eight of the excluded articles were conference abstracts not published elsewhere.
Characteristics of Included Trials

The 3 RCTs were all head-to-head comparisons of an intensive intervention compared with a minimal intervention.\textsuperscript{37-39} Two RCTs were pilot studies assessing feasibility and acceptability.\textsuperscript{37,39}

Sample sizes ranged from 17 to 333 participants that were predominately middle-aged African American women. The percentage of African Americans ranged from 71\% to 93\%; and women made up 69\% to 82\% of participants. Mean age ranged from 33 to 47 years. There were no subgroup analyses by age, gender, or race. All participants in the RCTs had persistent asthma and were prescribed an inhaled corticosteroid.\textsuperscript{37-39} The pre/post study targeted hospitalized asthmatics (Table 2).\textsuperscript{40}

Intervention Characteristics

Interventions were heterogeneous and focused on problem solving\textsuperscript{38}, self-efficacy\textsuperscript{39}, the use of patient advocates\textsuperscript{37}, and a pharmacist-led education intervention.\textsuperscript{40}

The patient advocate intervention included preparing patients for provider visits, attending one visit, confirming understanding of issues discussed during the visit, facilitating return appointments and following up with patients between visits. College educated lay staff members implemented the intervention.\textsuperscript{37}

The problem solving intervention was a motivational technique to train patients to view problems as “inevitable, normal, and solvable”.\textsuperscript{38} It consisted of four 30-minute sessions tailored to the specific adherence barriers of each patient. College educated lay staff members taught problem solving skills as way to combat medication
nonadherence and had subjects apply problem-solving skills to other areas in their lives to help solidify real-world application of skills.\textsuperscript{38}

The self-efficacy intervention coupled clinic-based group sessions with home visits to teach asthma self-efficacy skills.\textsuperscript{39} The intervention included four group sessions on asthma management, stress, physical activity and social support and 4 to 6 community health worker home visits focusing on the patient’s asthma status, asthma facts, medications, communication with providers, asthma triggers and cigarette smoke avoidance. The group session were implemented by social workers and the home visits by community health workers.\textsuperscript{39}

The pre/post pharmacist intervention consisted of a 30-minute in hospital counseling session covering asthma basics, signs and symptoms of exacerbations, disease triggers, peak flow monitoring, role of medications and spacers, and adverse effects of therapy. Pharmacists reinforced counseling, by phone, at one and five weeks after discharge.\textsuperscript{40}

Two of the four interventions were informed by qualitative analysis.\textsuperscript{37,39} The self-efficacy trial used self-efficacy and social learning theory, qualitative analysis and cultural adaption to inform intervention development.\textsuperscript{39} The patient advocate trial used qualitative analysis and cultural adaptation to inform the development of their intervention.\textsuperscript{37} However, the pre/post pharmacist intervention and problem solving trial did not report using behavior theory, qualitative analysis or cultural adaptation to inform the development of their interventions.\textsuperscript{38,40}
Comparators for the RCTs focused on asthma education in the form of mailed handouts\textsuperscript{39}, a CD\textsuperscript{37} or four 30-minute in-person sessions about asthma\textsuperscript{38}. All comparator interventions excluded topics of self-management or adherence. The pre/post study did not have comparators.\textsuperscript{40}

Time and Setting

All interventions were based in an urban health system and recruited from academic health centers and clinics serving uninsured and underinsured populations.\textsuperscript{37-39} Study duration ranged from 4 to 6 months.\textsuperscript{37-40}

Outcome Measures

All four studies measured adherence.\textsuperscript{37-39} The patient advocate and problem solving trials measured baseline adherence with a validated adherence questionnaire specifically designed for ICS and measured 30-day ICS adherence with an electronic actuation monitor.\textsuperscript{37,38} In both trials, two electronic ICS monitors were used because of the range in ICS devices (e.g., dry powder inhalers, HFA) used by patients. One device could identify dumping of medication by measuring the frequency and time of day of actuations and the other could only measure frequency of actuation. Adherence was measured monthly for 4-months in both trials.\textsuperscript{37,38}

The self-efficacy trial used a non-validated questionnaire to assess 14-day ICS adherence and was measured at baseline, 3 and 6 months.\textsuperscript{39} The pre/post pharmacist
intervention used percent of refills achieved within 10% of targeted refill dates to measure monthly and 6 month adherence.\textsuperscript{40}

In addition to adherence, included studies measured several other clinical health outcomes (e.g., FEV1, asthma control, asthma quality of life), health care utilization outcomes (e.g., any ED visit, asthma related ED visit) and intermediate health outcomes (e.g. asthma self-efficacy, asthma knowledge). Results are described below.

Adherence

All four studies measured adherence defined as 30-day adherence\textsuperscript{37,38}, 14-day adherence\textsuperscript{39}, or percent refills achieved within 10% of targeted refill dates\textsuperscript{40}. Among all three RCTS, none reported a statistically significantly difference between the intervention and comparator groups.\textsuperscript{37-39} For the pre/post pharmacist intervention, measuring timely refills, they reported a statistically significant increased mean adherence rate (SD) of 22% (6) to 63% (24) over 6 months, p=0.0175.\textsuperscript{40}

Asthma Health Outcomes

All three RCTs measured asthma control\textsuperscript{37-39}, FEV1\textsuperscript{37,38}, and asthma quality of life (AQLQ)\textsuperscript{37-39}. Most outcomes were not statistically significant. However, the self-efficacy trial found a statistically significant improvement in asthma quality of life (AQLQ), measured by mini-AQLQ, in the intervention arm versus the comparator arm (adjusted difference between groups: 1.8, p=0.002). The difference was clinically significant (greater than 0.5) and adjusted for baseline characteristics and propensity
scores.39 The pre/post pharmacist intervention did not measure asthma health outcomes.40

Health Care Utilization Outcomes

The patient advocate, problem solving and pre/post pharmacist interventions measured health care utilization outcomes.37,38,40 The pre/post pharmacist study reported a statistically significantly lower rate of asthma-related ED or hospital visits after patients received the intervention, mean visits (SD) 1.58 (1.13) to 0.35 (0.62), p=0.0016. 40

The patient advocate and problem solving trials did not find a statistically significant difference in asthma-related or any-cause emergency department visits or hospitalizations between patients in the intervention and comparator arms.37,38

Intermediate Outcomes

The self-efficacy trial was the only trial to measure intermediate outcomes (i.e., asthma knowledge and self-efficacy) other than adherence.39 The authors developed and validated a self-efficacy measure adapted from existing self-efficacy scales. They reported a transient increase in self-efficacy with a 3-month adjusted difference 0.8 (p <0.001; 95% CI, 0.4-1.3), but had a non-significant difference at 6 months. There was no change in asthma knowledge.39

Study Quality
We rated all three RCTs as medium risk of bias\textsuperscript{37-39} and the pre/post study as high risk of bias.\textsuperscript{40} The pre/post study received high risk of bias due to its susceptibility to selection bias and moderate detection bias due to the use of self-reported outcome measures.

The patient advocate and problem solving trials were rated as medium risk of bias due to attrition and measurement bias but both trials adequately adjusted for missing data using linear mixed effects modeling.\textsuperscript{37,38} In the patient advocate trial, 272 (68\%) adherence outcomes were recorded. Of the 128 that were missing, 48 (37\%) were due to equipment failure, 50 (39\%) due to monitor not returned and for 30 (23\%) due to the patient never bringing in a medication to attach the monitor. There was no difference in distribution of missing adherence data by treatment group.\textsuperscript{37}

The problem solving trial had similar issues. Adherence monitor downloads failed in 380 (20\%) of 2360 downloads, 18\% of the intervention group and 22\% of the control.\textsuperscript{38} Failures were again attributed to monitor failure, battery failure, and proximity to other batteries or magnets (Table 3).\textsuperscript{38}

\textbf{Discussion}

Among over 1460 studies screened, we identified four studies in the literature examining patient and family-level pharmacotherapy adherence interventions for adult AA. Three had small sample sizes,\textsuperscript{37,39,40} three were RCTs\textsuperscript{37-39} and one had high risk of bias due to study design.\textsuperscript{40} Among the interventions, only the pre/post pharmacist-led intervention was effective in improving adherence and reducing health care utilization; however, it targeted hospitalized asthmatics and at least half were not on ICS on
The other trials targeted persistent asthmatics that were prescribed ICS. These trials showed no improvement in adherence, asthma control, FEV1, or asthma knowledge. One of these studies, designed to improve asthma self-efficacy, reported improved asthma quality of life but no long-term change in asthma self-efficacy.

The lack of effectiveness of interventions could be due to several factors. First, the active controls could have mitigated the effect size. The problem solving study noted an overall improvement in asthma control, AQLQ, and FEV1. The authors ascribed the improvement in clinical outcomes to 66% of the control group thinking that the goal of the basic asthma education program (control arm) was to educate individuals on the importance of medication adherence. Second, the Hawthorne effect could have affected outcomes. Monitoring adherence with an electronic counter is not a benign intervention and can stimulate adherence in the control arm and reduce effect size. Third, only the problem solving study was powered to detect a change in adherence. The patient advocate and self-efficacy trials were feasibility and acceptability trials that were not powered to see changes in clinical outcomes.

Our results are consistent with findings in other systematic reviews. Press et al., found a paucity of interventions targeting adult AA asthmatic interventions and few rigorous study designs. A 2014 Cochrane review also confirmed that there were few RCTs that improved adherence and clinical outcomes. However an AHRQ systematic review found that policy interventions were most effective at improving adherence across conditions and included interventions to reduce copayments, improve prescription coverage, case management interventions, and patient-level education.
interventions with behavioral support.  

Future studies are needed focusing on quality adherence clinical trials in high-risk populations such as adult AA. We recommend increasing the measure of adherence as a secondary outcome in clinical trials to supplement the observational literature, the use of objective measures of adherence, the integration of education, behavioral and policy approaches to improve adherence and clinical outcomes, and the use of behavior theory and qualitative methods to inform study design. Lastly, there needs to be an exploration of the unique barriers and facilitators to high-risk populations’ response to standard adherence interventions.

There are a few limitations of our review. First, publication bias may limit our findings. However, we reviewed conference abstracts to minimize publication bias. Second, we were not able to perform a meta-analysis due to the heterogeneity of interventions. Third, we limited to studies with “African American” search terms and at least 30% AA. Using the “African American” search term could have excluded studies that did not focus on asthma disparities or high-risk populations. However, we supplemented the database searches and conference abstracts with a review of prior medication adherence systematic reviews and minority asthma intervention systematic reviews. Limiting to 30% could have excluded studies but a prior systematic review of asthma interventions in minorities used 50% as a limit. We used 30% as conservative limit between the national percentage of AA (13.2%) and the limit used in a prior review (50%).

In conclusion, few studies assessing asthma adherence interventions focused on adult AA populations. Data from one RCT suggests that interventions focused on self-
efficacy improve asthma related quality of life compared with controls. Although one pre/post study found improved adherence with a pharmacist-led intervention, none of the 3 included RCTs demonstrated improved adherence in participants randomized to an active intervention compared with controls. Future studies are needed which use rigorous study design, are informed by theory and qualitative data, and integrate education, behavioral and policy approaches to improve adherence and clinical outcomes and reduce health disparities.
Figure 1: Analytic framework for interventions to improve adherence to asthma pharmacotherapy in adult African American asthmatics

Key Question: What patient and family level interventions are effective in improving patient adherence to asthma pharmacotherapy in adult Black/African Americans?
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<th>Table 1: Inclusion and Exclusion Criteria</th>
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<tr>
<td><strong>Inclusion</strong></td>
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<td><strong>P-population</strong></td>
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<td>1. Asthmatics (at least 80% of study</td>
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<td>2. Age 18 years or older</td>
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<td>3. Mixed adult and pediatric populations when authors report outcomes separately for pediatric and adult groups or if at least 80% are adults</td>
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<td>4. At least 30% Black/African American study population</td>
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<td>5. Less than 30% Black/African American when subgroup analysis is performed</td>
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<tr>
<td><strong>I-intervention</strong></td>
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<tr>
<td>1. Asthma pharmacotherapy adherence</td>
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<td>promotion intervention</td>
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<td>- Example: medication reminder system, multi-component intervention that measures asthma pharmacotherapy adherence</td>
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<td>2. Family and/or patient level</td>
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<td><strong>C-comparator</strong></td>
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<td>1. Active or usual care comparator</td>
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<td>Primary Outcome: Any measure of</td>
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<td>Secondary Outcomes:</td>
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<td>1. Health outcomes- any measures of</td>
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<td>2. Health utilization outcomes- any use</td>
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<td>3. Intermediate outcomes- asthma</td>
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<td>T-time previous time over which to review literature</td>
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Figure 2: Article Review Flow Diagram

**2628 Original Search Results**
- 552 PubMed
- 880 EMBASE
- 349 CINAHL
- 848 WOS

**1168 Duplicates**

**1461 Title Abstract Review**

**1291 Excluded**

**Full Text Review**
- Title Abstract Review: 170
- References: 1

**4 Included in Analysis**

**Exclusion Criteria**
- Population: 28
- Intervention: 69
- Outcome: 37
- Time: 3
- Setting: 13
- Study Design: 2
- Other*: 15

EMBASE- Excerpta Medica dataBASE, WOS - Web of Science, CINAHL - Cumulative Index to Nursing and Allied Health Literature

*Other: 1 full text unavailable, 2 duplicates, 4 full text included in search results, 8 conference abstracts with insufficient information