



Canadian Agency for  
Drugs and Technologies  
in Health

## RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL



**TITLE: Montelukast for Sleep Apnea: A Review of the Clinical Effectiveness, Cost Effectiveness, and Guidelines**

**DATE:** 17 January 2014

### CONTEXT AND POLICY ISSUES

Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent episodes of partial (hypopnea) or complete (apnea) upper airway obstruction during sleep despite ongoing respiratory efforts, resulting in disruption of sleep (arousal).<sup>1</sup> OSA affects 9% of middle-aged men and 3% of women in North America.<sup>2</sup> In children, the prevalence ranges between 1% to 5% depending on the diagnostic criteria.<sup>3</sup> If left untreated, OSA can lead to fatigue, somnolence, headaches, cardiovascular disease, decreased quality of life, and increased risk of motor vehicle accidents.<sup>2</sup>

The gold standard assessment for OSA is polysomnography, a test that measures neurologic and cardio-respiratory parameters during sleep.<sup>1,2</sup> The frequency of obstructive events measured during polysomnography is reported as the apnea-hypopnea index (AHI).<sup>2</sup> According to the American Academy of Sleep Medicine, the severity of OSA is defined by the following AHI cut-offs: mild,  $\geq 5$  and  $< 15$  events/hour; moderate,  $\geq 15$  and  $< 30$  events/hour; severe,  $\geq 30$  events/hour.<sup>1</sup> OSA is often accompanied by clinical symptoms such as excessive daytime sleepiness, behavioural and mood problems, morning headaches, and difficulty concentrating.<sup>3,4</sup>

Treatment options for OSA include weight loss, dental devices or oral appliance therapy, surgical procedures, and continuous positive airway pressure (CPAP).<sup>2</sup> Adenotonsillectomy is the primary treatment for children with adenotonsillar hypertrophy, the most common underlying risk factor for the development of pediatric OSA.<sup>3</sup> Surgical procedures can be painful and post-operative complications may occur, making non-invasive treatments a useful option for patients contraindicated for surgery or who have residual OSA after surgery.<sup>5</sup>

Leukotrienes are inflammatory mediators in the respiratory system and are involved in the propagation of inflammation in children with OSA.<sup>3,6</sup> Elevated levels of leukotriene receptors were found in tonsils from children with OSA.<sup>6</sup> Montelukast (Singulair) is a leukotriene receptor antagonist used as therapy for asthma and allergic rhinitis and has been considered as a therapy option for children with mild OSA due to its anti-inflammatory properties.<sup>3</sup>

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The purpose of this review is to examine the clinical effectiveness, cost effectiveness and guidelines regarding the use of montelukast for the treatment of sleep apnea.

**RESEARCH QUESTIONS**

1. What is the clinical effectiveness of montelukast for the treatment of sleep apnea?
2. What is the cost effectiveness of montelukast for the treatment of sleep apnea?
3. What are the evidence-based guidelines for the use of montelukast for the treatment of sleep apnea?

**KEY FINDINGS**

One study found that montelukast improved respiratory disturbances in children with mild to moderate obstructive sleep apnea (OSA). No published trials regarding the use of montelukast in adults with OSA were identified. No economic evaluations or evidence-based guidelines regarding the use of montelukast for the treatment of sleep apnea were identified.

**METHODS**

**Literature Search Strategy**

A limited literature search was conducted on key resources including MEDLINE and Embase via Ovid, PubMed, The Cochrane Library (2013, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between January 1, 2008 and December 11, 2013.

**Selection Criteria and Methods**

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Adult or pediatric patients with sleep apnea
<b>Intervention</b>	Montelukast (Singulair)
<b>Comparator</b>	Placebo, continuous positive airway pressure (CPAP), surgical interventions
<b>Outcomes</b>	Clinical effectiveness (symptom reduction, changes in sleep profile, quality of life, safety), Cost effectiveness, Guidelines and Recommendations
<b>Study Designs</b>	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, evidence-based guidelines and economic evaluations

## Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, or were published prior to 2008.

## Critical Appraisal of Individual Studies

The quality of included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.<sup>7</sup> RCT study quality was evaluated using the Downs and Black instrument.<sup>8</sup> A numeric score was not calculated for each study. Instead, strengths and limitations of each study were summarized and described.

## SUMMARY OF EVIDENCE

### Quantity of Research Available

The literature search yielded 31 citations. Upon screening titles and abstracts, 26 citations were excluded and five potentially relevant articles were retrieved for full-text review. No additional potentially relevant reports were identified through grey literature searching. Of the five potentially relevant reports, three did not meet the inclusion criteria. Two reports were included in this review. The study selection process is outlined in a PRISMA flowchart (Appendix 1). One systematic review and one randomized controlled trial met inclusion criteria. No economic evaluations or guidelines were identified.

### Summary of Study Characteristics

Details on study characteristics can be found in Appendix 2.

#### *Country of origin*

The authors of the systematic review were from Germany and Canada.<sup>5</sup> The RCT was conducted in Israel.<sup>6</sup>

#### *Study design*

One systematic review of RCTs<sup>5</sup> and one randomized, double-blind, placebo-controlled trial<sup>6</sup> was included. The systematic review searched for RCTs that were published up until 2010. The RCT was identified in the systematic review, but there was insufficient data at the time of publication for adequate analysis as only an abstract was available.

#### *Patient population*

The systematic review included RCTs of children between one and 16 years of age with OSA as diagnosed by polysomnography (AHI  $\geq$  1/hour).<sup>5</sup> The RCT included children between 2 and 10 years of age with mild to moderate OSA as diagnosed by polysomnography (AHI  $<$  10/hour) that had not received adenotonsillectomy in the past.<sup>6</sup> No evidence on the use of montelukast in adults was identified.

### *Interventions and comparators*

The systematic review looked at RCTs of anti-inflammatory drugs including steroids, leukotriene receptor antagonists ketotifen and chromones.<sup>5</sup> The RCT compared a treatment regimen of 4 mg (< 6 years old) or 5 mg (> 6 years old) oral montelukast once-daily for 12 weeks to placebo.

### *Outcomes measured*

The systematic review and RCT looked at the apnea-hypopnea index (AHI) as an outcome which measures the number of apnea and hypopnea episodes per hour. The RCT also looked at obstructive apnea index (OAI), which measures the number of apnea events per hour,<sup>6</sup> and evaluated the adenoid size using the adenoidal nasopharyngeal ratio.<sup>6</sup>

## **Summary of Critical Appraisal**

Details of critical appraisal can be found in Appendix 3.

The systematic review employed a comprehensive literature search that included grey literature, screened in duplicate, and assessed the scientific quality of included studies.<sup>5</sup> A summary of the characteristics of included and excluded studies were provided. The risk of publication bias was not formally assessed.

The RCT reported an adequate method of randomization, with both patient and outcome assessors blinded.<sup>6</sup> A power calculation was performed to determine an adequate sample size for detecting clinically significant differences. Enrolled patients had mild to moderate sleep apnea, which may limit generalizability of results to patients with more severe forms of sleep apnea. In addition, included patients had not undergone adenotonsillectomy, the primary treatment for children with OSA, which may not be reflective of clinical practice.

## **Summary of Findings**

Details on study findings can be found in Appendix 4.

### What is the clinical effectiveness of montelukast for the treatment of sleep apnea?

The systematic review identified one RCT that used montelukast for the treatment of children with sleep apnea.<sup>5</sup> At the time of publication, however, this study was only published as an abstract that contained insufficient information for data analysis, and so the results were not considered in the discussion. This randomized, double-blind, placebo-controlled trial has since been published and is included in this review.<sup>6</sup>

The RCT found that oral montelukast, when administered over a period of 12 weeks, improved respiratory disturbances in children with mild to moderate OSA as determined by the AHI and OAI.<sup>6</sup> The AHI and OAI scores remained unchanged after treatment in the placebo group. There was a statistically significant improvement in the OAI after montelukast treatment ( $P < 0.01$ ), while the improvement in AHI was not statistically significant ( $P = 0.07$ ). There was also a statistically significant reduction in the size of adenoid tissues after treatment in the montelukast group as determined by the adenoidal nasopharyngeal ratio ( $P < 0.001$ ), while there was no change in the placebo group. No adverse events were reported during the study period.

What is the cost effectiveness of montelukast for the treatment of sleep apnea?

No evidence on the cost effectiveness of montelukast for the treatment of sleep apnea was identified.

What are the evidence-based guidelines for the use of montelukast for the treatment of sleep apnea?

No evidence-based guidelines for the use of montelukast for the treatment of sleep apnea were identified.

### **Limitations**

In the systematic review, there was limited data on the effectiveness of montelukast in children with sleep apnea. In the RCT, only children with mild to moderate OSA were enrolled, limiting the generalizability of the results to a broader population. In addition, no published studies were identified that examined the use of montelukast in adults with OSA.

The included RCT had a sample size of 46 patients, and although this was adequately powered to show a difference between treatment groups, there is a need for larger-scale studies.<sup>6</sup> This study also used placebo as a comparator rather than adenotonsillectomy, a commonly recommended therapy for children with OSA. This comparison is problematic as it is not reflective of clinical practice. In addition, it is unclear whether the improvement in respiratory disturbances is linked to improvements in quality of life, as this outcome was not evaluated.

There was no evidence on the cost effectiveness of montelukast for the treatment of sleep apnea or evidence-based guidelines regarding the use of montelukast for the treatment of sleep apnea identified.

### **CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING**

According to one RCT, oral montelukast appears to be effective at improving respiratory disturbances in children with mild to moderate OSA as determined by improvements in AHI and OAI scores. The effect of these improvements on quality of life outcomes was not evaluated.

No published trials regarding the use of montelukast in adults with OSA were identified in this review. There is one study in adult patients with OSA that is comparing the use of oral montelukast in combination with budesonide nasal spray to placebo that was expected to be completed in December 2013.<sup>9</sup>

No published trials comparing montelukast to other active treatments were identified in this review. One study comparing montelukast to budesonide nasal spray in children with mild to moderate OSA that appears to be completed with no published results.<sup>10</sup>

No evidence was identified regarding the cost effectiveness of montelukast for the treatment of sleep apnea. No evidence-based guidelines were identified regarding the use of montelukast for the treatment of sleep apnea.

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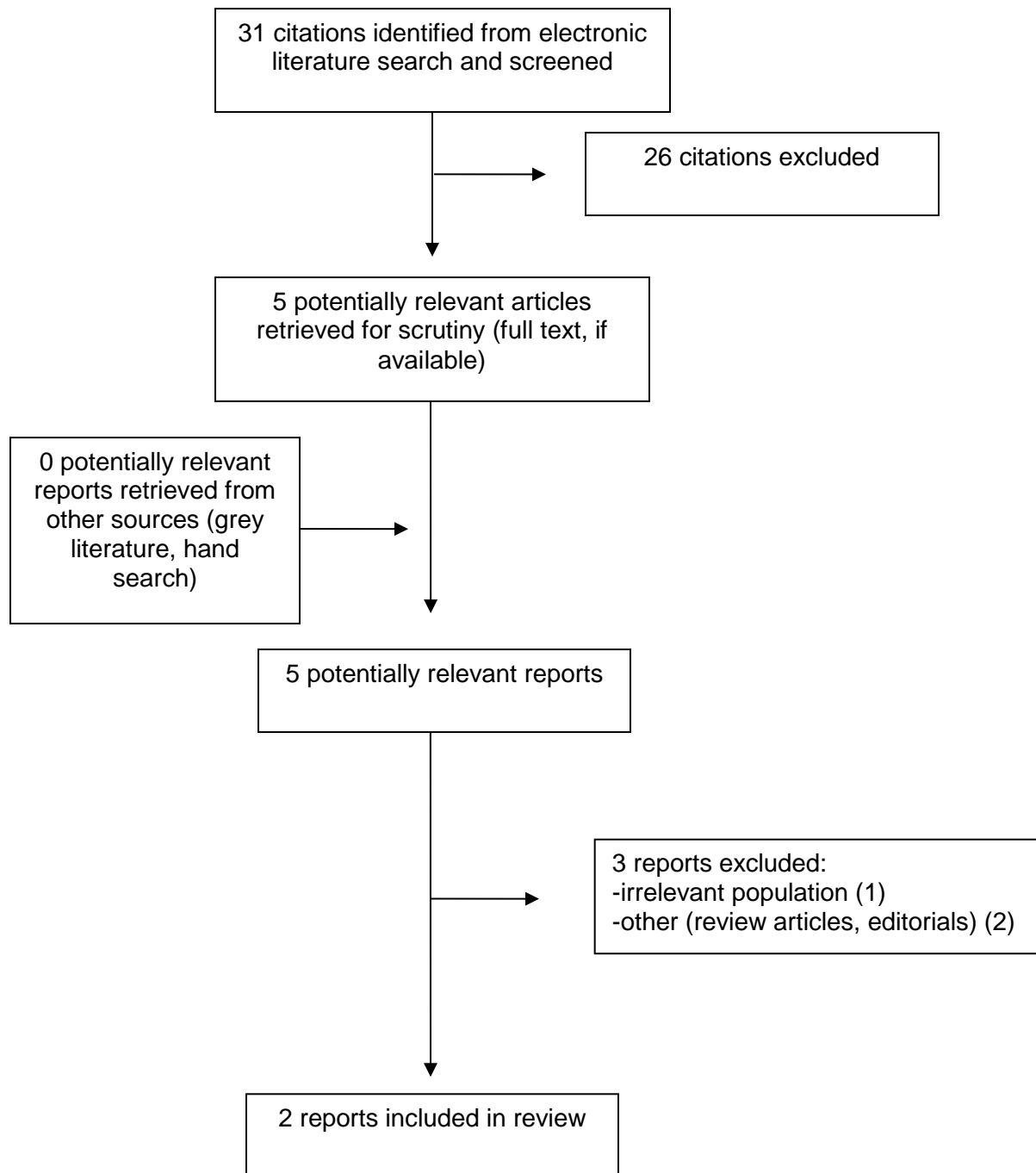
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APPENDIX 1: Selection of Included Studies





**APPENDIX 2: Summary of Study Characteristics**

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention and Comparator(s)	Clinical Outcomes Measured
Kuhle <sup>9</sup> 2011 Germany and Canada	Systematic review of RCTs	Children between one and 16 years of age with objectively diagnosed OSA (AHI $\geq$ 1/h)	Anti-inflammatory drugs (steroids, leukotriene receptor antagonists, ketotifen, cromones)	AHI
Goldbart <sup>6</sup> 2012 Israel	Double-blind, randomized, placebo-controlled study  12 weeks	46 children 2 to 10 years with mild to moderate OSA (AHI < 10/h) that had not received adenotonsillectomy in the past	4 mg (<6 years) or 5 mg (>6 years) montelukast orally once-daily (n=23)  Placebo (n=23)	AHI, OAI

AHI = apnea hypopnea index; OAI = obstructive apnea index; RCT = randomized controlled trial

**APPENDIX 3: Summary of Critical Appraisal**

First Author, Publication Year, Study Design	Strengths	Limitations
Kuhle <sup>9</sup> 2011  Systematic review	<ul style="list-style-type: none"> <li>• Comprehensive literature search based on clearly defined objectives</li> <li>• Summary of study characteristics and list of included and excluded studies provided</li> <li>• Grey literature was included in the search strategy</li> </ul>	<ul style="list-style-type: none"> <li>• Publication bias not assessed</li> </ul>
Goldbart <sup>6</sup> 2012  RCT	<ul style="list-style-type: none"> <li>• Method of randomization described</li> <li>• Power calculation was performed to determine adequate sample size</li> <li>• Patients and outcome assessors blinded</li> <li>• All patients received assigned treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Enrolled patients had mild to moderate sleep apnea, limiting generalizability to patients with more severe conditions</li> </ul>

APPENDIX 4: Summary of Findings

First Author, Publication Year, Study Design	Main Study Findings	Author's Conclusions
<p>Kuhle<sup>9</sup> 2011</p> <p>Systematic review</p>	<p>One study used montelukast for the treatment of children with sleep apnea (Goldbart 2012),<sup>6</sup> described below, but was only published as an abstract at the time the systematic review was conducted. The abstract reported only a before-after comparison for the montelukast group. In the absence of a valid comparison, the authors did not include data from the trial in the analysis.</p> <p>One study each looked at the effectiveness of fluticasone and budesonide for the treatment of children with sleep apnea.</p>	<p>“There is insufficient evidence to comment on the effect of oral leukotriene receptor antagonists in children with mild OSA. Further RCTs are needed to evaluate anti-inflammatory drugs for OSA in children.” (p. 8)</p>
<p>Goldbart<sup>6</sup> 2012</p> <p>RCT</p>	<p><u>Montelukast group – mean AHI (SD), events per hour</u> Pre: 6.0 (3.2) Post: 3.6 (2.3) P=0.07</p> <p><u>Placebo group – mean AHI (SD), events</u> Pre: 5.7 (3.2) Post: 6.1 (3.4) Not significant</p> <p><u>Montelukast group – mean OAI (SD), events per hour</u> Pre: 3.9 (1.6) Post: 1.7 (1.0) P&lt;0.01</p> <p><u>Placebo group – mean OAI (SD), events per hour</u> Pre: 3.5 (1.6) Post: 3.7 (1.0) Not significant</p> <p><u>Montelukast group – mean adenoidal nasopharyngeal ratio (SD)</u> Pre: 0.81 (0.04) Post: 0.57 (0.04) P&lt;0.001</p> <p><u>Placebo group – mean adenoidal nasopharyngeal ratio (SD)</u> Pre: 0.77 (0.05) Post: 0.76 (0.03) Not significant</p> <p>No adverse events were reported during the study period.</p>	<p>“This study showed that oral montelukast, administered over a period of 12 weeks in children with OSA, effectively alleviated the severity of nocturnal respiratory disturbance, reduced the size of adenoid tissues, and significantly improved sleep symptoms. Furthermore, the treatment was not associated with any side effects and was well tolerated.” (p. e578)</p>

AHI = apnea hypopnea index; OAI = obstructive apnea index; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SD = standard deviation