Therapeutic effects of different drugs on obstructive sleep apnea/hypopnea syndrome in children

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Background: **This study aimed to compare the therapeutic effects of different drugs on obstructive sleep apnea/hypopnea syndrome (OSAHS) in children by using a network meta-analysis approach.**

Methods: **PubMed, Embase and Cochrane Library were searched from the inception of each database to November 2015. Randomized controlled trials (RCTs) concerning the comparisons in the therapeutic effects of eight placebo-controlled drugs on OSAHS in children were included in this study. Network meta-analysis combined direct evidence and indirect evidence to evaluate the weighted mean difference (WMD) and surface under the cumulative ranking curves (SUCRA) of therapeutic effects of eight drugs on OSAHS in children.**

Results: **A total of seven RCTs were finally incorporated into our network meta-analysis. Pairwise meta-analysis results revealed that therapeutic effect of placebo was significantly poorer than that of intranasal mometasone furoate, montelukast, budesonide and fluticasone concerning apnea hypopnea index (AHI) value [WMD=1.40, 95% confidence interval (CI)=1.17-1.63; WMD=2.80, 95% CI=1.01-4.59; WMD=3.50, 95% CI=3.34-3.66; WMD=7.20, 95% CI=5.26-9.14, respectively], and fluticasone is better than placebo concerning sleep efficiency (WMD=3.50, 95% CI=2.42-4.58); regarding visual analogue scale, the therapeutic effect of placebo was poorer compared with sucralfate and clindamycin (WMD=1.94, 95% CI=1.13-2.75; WMD=1.06, 95% CI=0.22-1.90), and sucralfate is better than clindamycin (WMD=-0.88, 95% CI=-1.65 to -0.11). However, network meta-analysis results showed no obvious difference in the therapeutic effects of different drugs on OSAHS regarding AHI and sleep efficiency. Furthermore, the best SUCRA value was very high for fluticasone concerning AHI (86.6%) and budesonide concerning sleep efficiency (94.0%) for OSAHS treatment.**

Conclusion: **Fluticasone and budesonide have relatively good effects in the treatment of OSAHS in children, thus providing an important guiding significance for the treatment of OSAHS in children.**

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Key words: **apnea hypopnea index; Bayesian network model; obstructive sleep apnea/hypopnea syndrome; randomized controlled trials; sleep efficiency**

Introduction

Obstructive sleep apnea/hypopnea syndrome (OSAHS) is a sleep respiratory disorder caused by complete or partial obstructions of the upper airway, and is characterized by repetitive episodes of shallow or paused breathing during sleep.[1] OSAHS is increasingly recognized in children with an estimated rate of 1%-3%; and the peak age is 2-5 years. Long-term disease results in all-systemic symptoms, cardiovascular complications, developmental inhibition and cognitive dysfunction.[2,3] Surgical treatment is considered as the most common therapeutic intervention for OSAHS but with perioperative risk and high recurrence rate, thus non-surgical treatment modalities have become an increased interest recently.[4] As non-surgical alternatives for treating OSAHS in children has achieved good effects, and adequate postoperative drug therapy can help prevent recurrence after surgery.[5] In addition, drug therapy is non-invasive with many drugs as the choice for treating OSAHS in children, though without agreement on the treatment selection.[6,7]

To determine the optimal therapy strategy for OSAHS, several parameters were applied for evaluation of therapeutic efficiency, including apnea hypopnea

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index (AHI), sleep efficiency and visual analogue scale (VAS). AHI computed as the total of apneas and hypopneas divided by the total sleep time in hours is an index used to indicate the severity of sleep apnea.[8] VAS is a psychometric response scale which can be used in questionnaires for subjective characteristics or attitudes that cannot be directly measured.[9] Sleep efficiency was calculated as the ratio of total sleep time to time in bed.[10] In medical research, placebos are considered as an important methodological tool, and placebo-controlled studies are used to test medical therapy.[11] Treating allergic rhinitis with nasal steroid has positive effects both on OSAHS and daily activity.[12] The use of non-surgical treatment for childhood OSA is gaining popularity, especially in children with mild disease, four months of treatment with intranasal mometasone furoate (IMF) effectively reduces the severity of mild OSA in children compared with placebo.[13] Topical sucralfate and clindamycin have been indicated as safe drugs without important adverse effects in the reduction of post-tonsillectomy pain in children aged 6-12 years suffering from sleep apnea or snoring.[14] A one-time preoperative oral dose of pregabalin and celecoxib before adult maxillomandibular advancement surgery for OSA decreased mean intravenous morphine consumption, daily narcotic pill consumption, and patient perceived pain.[15] A previous meta-analysis analyzed three studies comparing the efficacy of anti-inflammatory drugs for the treatment of OSA in children, including intranasal fluticasone versus placebo, intranasal budesonide versus placebo, oral montelukast versus placebo, and only single small study has found a short-term beneficial effect of intranasal budesonide over placebo in reducing AHI in children with mild to moderate OSA.[16] Caffeine may lead to snoring in preterm infants, but therapeutic administration of neonatal caffeine brings no long-term effects on administration sleep apnea when compared with placebo.[17,18] Up to now, no consensus has been reached on the optimal drug therapy in the treatment of OSAHS. Network meta-analysis is a relatively new statistical technique that gives access to compare both direct and indirect evidences, even when two of the interventions have not been directly compared.[19] Network meta-analysis can summarize randomized controlled trials (RCTs) of several different treatment strategies, and supply point estimates for their association with a given endpoint, together with an estimate of incoherence. Therefore, we performed a network meta-analysis to compare the therapeutic effects of different drugs on OSAHS in children by using a network meta-analysis approach, including placebo, IMF, caffeine, montelukast, budesonide, fluticasone, pregabalin plus celecoxib, sucralfate and clindamycin with AHI, sleep efficiency and VAS as endpoints.

Methods

Literature search

Computer retrieval was carried out on PubMed, Embase and Cochrane Library, and other related references were supplemented by manual retrieval from the inception of each database to November 2015 using combination of keywords and free words. Search terms mainly include: obstructive sleep apnea hypopnea syndrome (OSAHS), drug therapy, randomized controlled trial (RCT), etc.

Inclusion and exclusion criteria

Literature inclusion criteria: 1) study design: RCT; 2) interventions: placebo, IMF, caffeine, montelukast, budesonide, fluticasone, pregabalin plus celecoxib, sucralfate and clindamycin; 3) study subjects: children (3-12 years old) diagnosed with OSAHS; 4) outcomes: literature contains outcomes such as AHI, sleep efficiency and VAS; 5) relevant literature analyzing the treatment effects of OSAHS. Literature exclusion criteria: 1) children with hereditary syndrome, congenital or acquired neurological diseases, neuromuscular diseases or craniofacial anomalies; 2) children previously treated with upper airway surgery; 3) children with known fixed nasal obstruction such as previous nasal fracture or deviated nasal septum; 4) studies lacking sufficient data (e.g., non-paired studies); 5) non-RCTs; 6) duplicated publications; 7) conference report, system evaluation or abstract article; and 8) non English studies.

Data extraction and quality evaluation

Two reviewers extracted data from the enrolled studies using a specifically designed form. If there was a dispute in the process of data extraction, we would discuss and reach a consensus through consultation with a number of researchers. RCTs were evaluated by more than two researchers based on the Cochrane risk of bias assessment tool.[20] In assessment, a judgment was assigned as "yes", "no" or "unclear" for each domain to designate a low, high or unclear risk of bias, respectively. If one or no domain was deemed "unclear" or "no", the study was classified into low risk of bias. If four or more domains are deemed "unclear" or "no", the study was classified into a high risk of bias. If two or three domains were deemed "unclear" or "no", the study was classified into a moderate risk of bias.[21] Quality assessment and investigation of publication bias were carried out using Review Manager 5 (RevMan 5.2.3, Cochrane Collaboration, Oxford, UK).

Statistical analysis

First, traditional pairwise meta-analyses were carried out for studies with direct comparison of different treatment arms. We reported the results as weighted mean difference (WMD) or odds ratio (OR) with 95% confidence interval (CI) accounting for study sample sizes. Second, we used R software to draw network diagrams of various interventions and studies. Among them, each node represents each intervention, the node size represents the sample size, and the thickness of lines between nodes represents the number of included studies. Bayesian network meta-analyses were carried out to compare different interventions to each other. Each analysis was based on non-informative priors for effect sizes and precision. Convergence and lack of auto correlation were checked and confirmed after four chains and a 20 000-simulation burn-in phase; finally, direct probability statements were derived from an additional 50 000-simulation phase.[22] To assist in the interpretation of WMDs or ORs, we calculated the probability of each intervention being the most effective or safest treatment method based on a Bayesian approach using probability values summarized as surface under the cumulative ranking curve (SUCRA), the larger the SUCRA value, the better the rank of the intervention.[23,24] All computations were done using R (V.3.1.2) package gemtc (V.0.6), along with the Markov Chain Monte Carlo Engine Open BUGS (V.3.4.0).

Results

Baseline characteristics of included studies

Through electronic databases and manual search, 258 articles were retrieved; among them, 76 duplicates, 28 letters or reviews and 24 non-English studies were excluded; and the remaining 130 studies were further assessed. Then, 35 studies not relevant to OSAHS, 37 not relevant to treatment effect comparison, 47 not relevant to drug therapy and four without data or incomplete data were excluded. Eventually, seven RCTs were included into the network meta-analysis (Fig. 1).[13-15,18,25-27] These seven RCTs, published between 2001 and 2015, included 499 OSAHS children. Of the enrolled studies, four were from Caucasians, and three were from Asians; additionally, six studies were two-arm trials and one was three-arm trials. The baseline characteristics of included studies are displayed in Supplemental Table. Cochrane systematic bias evaluation is shown in Fig. 2.

Pairwise meta-analysis

At first, we carried out direct paired comparisons for the therapeutic effects of eight placebo-controlled drugs on OSAHS in children, including IMF, caffeine,

Table 1. Pairwise meta-analysis of three endpoint outcomes

Outcomes	Comparisons	Pairwise meta-analysis WMD (95% CI)
AHI	Placebo *vs*. IMF	1.40 (1.17, 1.63)
	Placebo *vs*. caffeine	0.00 (-0.04, 0.04)
	Placebo *vs*. montelukast	2.80 (1.01, 4.59)
	Placebo *vs*. budesonide	3.50 (3.34, 3.66)
	Placebo *vs*. fluticasone	7.20 (5.26, 9.14)
Sleep efficiency	Placebo *vs*. fluticasone	3.50 (2.42, 4.58)
	Placebo *vs*. montelukast	-0.90 (-4.26, 2.46)
	Placebo *vs*. budesonide	-4.10 (-5.17, -3.03)
VAS	Placebo *vs*. pregabalin plus celecoxib	1.20 (-1.53, 3.93)
	Placebo *vs*. sucralfate	1.94 (1.13, 2.75)
	Placebo *vs*. clindamycin	1.06 (0.22, 1.90)
	Sucralfate *vs*. clindamycin	-0.88 (-1.65, -0.11)

WMD: weighted mean difference; CI: confidence interval; AHI: apnea hypopnea index; IMF: intranasal mometasone furoate; VAS: visual analogue scale.

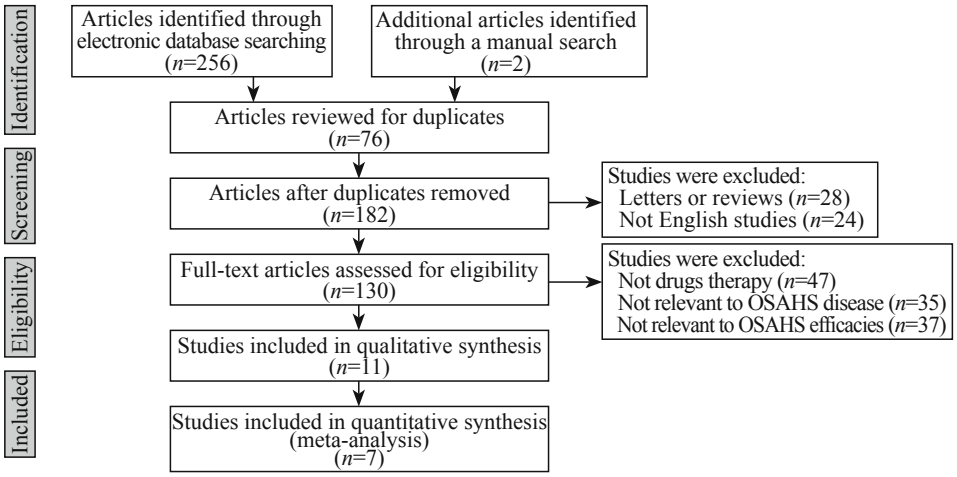

Fig. 1. Flow chart of literature screening. OSAHS: obstructive sleep apnea/hypopnea syndrome.

montelukast, budesonide, fluticasone, pregabalin plus celecoxib, sucralfate and clindamycin, and the results suggested that therapeutic effect of placebo was significantly poorer than that of IMF, montelukast, budesonide and fluticasone concerning AHI value (WMD=1.40, 95% CI=1.17-1.63; WMD=2.80, 95% CI=1.01-4.59; WMD=3.50, 95% CI=3.34-3.66; WMD=7.20, 95% CI=5.26-9.14, respectively), but fluticasone is better than placebo concerning sleep efficiency (WMD=3.50, 95% CI=2.42-4.58); for VAS, the therapeutic effect of placebo was poorer than that of sucralfate and clindamycin (WMD=1.94, 95% CI=1.13-2.75; WMD=1.06, 95% CI=0.22-1.90), but sucralfate is better than clindamycin (WMD=-0.88, 95% CI=-1.65 to -0.11) (Table 1).

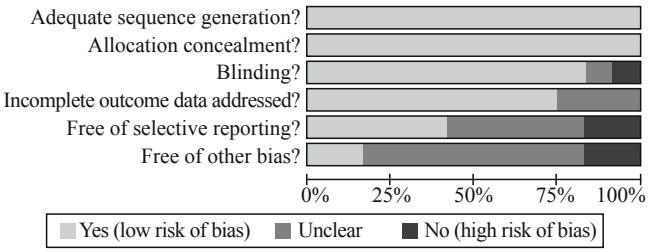

Fig. 2. Cochrane systematic bias evaluation chart of included studies.

Network relation evidence

In terms of AHI and sleep efficiency, the number of OSAHS children receiving placebo treatment is the largest among all the eight kinds of drugs (Fig. 3).

Main results of network meta-analysis and cumulative ranking probability

The network meta-analysis results showed no obvious difference in the therapeutic effects of different drugs on OSAHS regarding AHI and sleep efficiency (Table 2). Furthermore, with respect to AHI, SUCRA results demonstrated that fluticasone had the best effect for OSAHS treatment (86.6%) compared with placebo, IMF, caffeine, montelukast and budesonide; additionally, budesonide has the best effect on OSAHS concerning sleep efficiency (94.0%) compared with placebo, montelukast and fluticasone (Fig. 4).

Table 2. WMD (95% CI) of different treatment modalities of AHI and sleeping efficiency

AHI					
Placebo	-1.41 (-10.75, 7.68)	-0.00 (-8.93, 8.91)	-2.66 (-12.36, 6.25)	-3.52 (-12.71, 5.29)	-7.17 (-16.52, 2.31)
1.41 (-7.68, 10.75)	IMF	1.41 (-11.44, 13.89)	-1.21 (-14.61, 11.61)	-2.12 (-14.68, 10.82)	-5.84 (-18.64, 8.10)
0.00 (-8.91, 8.93)	-1.41 (-13.89, 11.44)	Caffeine	-2.67 (-15.76, 10.05)	-3.54 (-16.12, 9.61)	-7.22 (-19.97, 6.11)
2.66 (-6.25, 12.36)	1.21 (-11.61, 14.61)	2.67 (-10.05, 15.76)	Montelukast	-0.89 (-13.41, 12.25)	-4.53 (-16.99, 9.13)
3.52 (-5.29, 12.71)	2.12 (-10.82, 14.68)	3.54 (-9.61, 16.12)	0.89 (-12.25, 13.41)	Budesonide	-3.70 (-16.26, 9.91)
7.17 (-2.31, 16.52)	5.84 (-8.10, 18.64)	7.22 (-6.11, 19.97)	4.53 (-9.13, 16.99)	3.70 (-9.91, 16.26)	Fluticasone
Sleeping efficiency					
Placebo	-3.26 (-8.64, 2.14)	0.80 (-5.34, 6.92)	4.16 (-1.06, 9.32)	-	-
3.26 (-2.14, 8.64)	Fluticasone	4.03 (-3.68, 12.29)	7.47 (-0.16, 14.95)	-	-
-0.80 (-6.92, 5.34)	-3.26 (-8.64, 2.14)	Montelukast	3.36 (-4.56, 11.41)	-	-
-4.16 (-9.32, 1.06)	-7.47 (-14.95, 0.16)	-3.36 (-11.41, 4.56)	Budesonide	-	-

Comparison between treatments should be read from column to row. WMD: weighted mean difference; CI: confidence intervals; AHI: apnea hypopnea index; IMF: intranasal mometasone furoate; "-": no data.

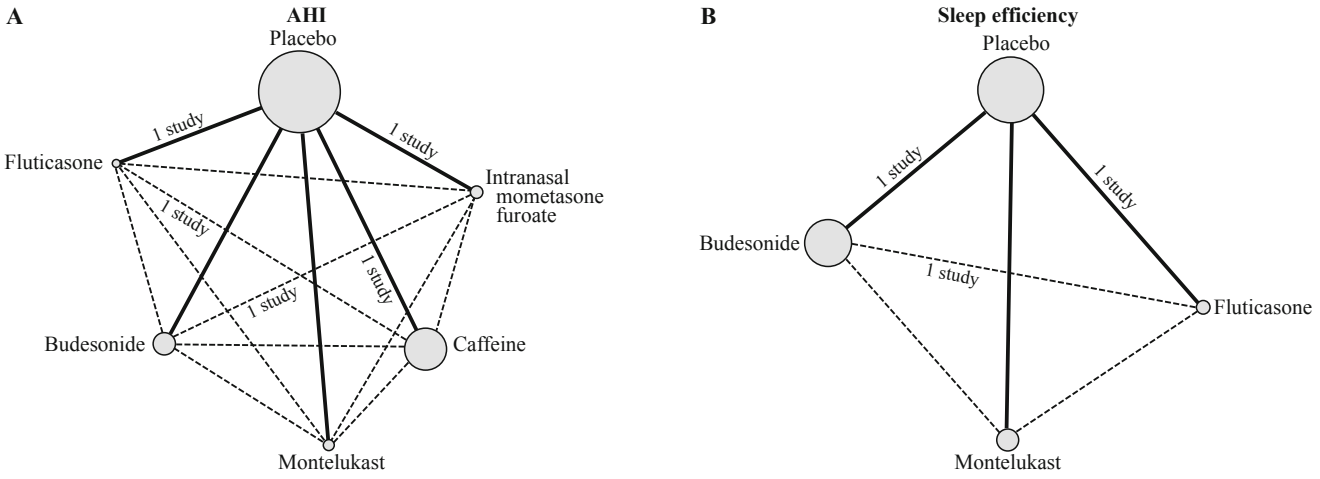

Fig. 3. Network relation evidence chart of different drugs on obstructive sleep apnea/hypopnea syndrome in children in terms of apnea hypopnea index (AHI) (**A**) and sleep efficiency (**B**).

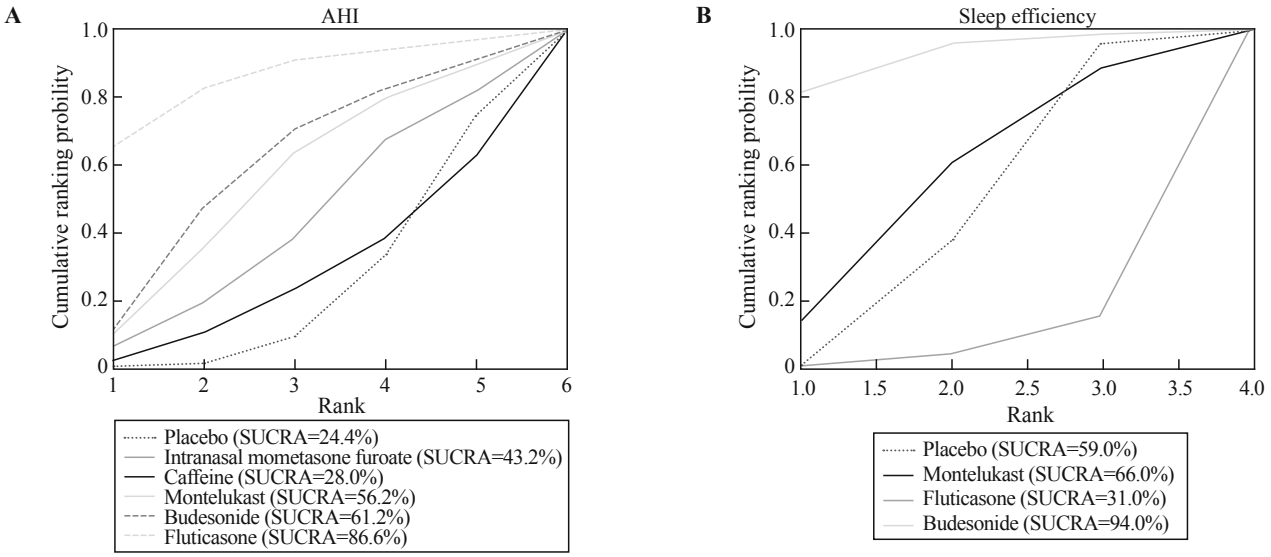

Fig. 4. Effects of different drugs on obstructive sleep apnea/hypopnea syndrome in children with respect to apnea hypopnea index (AHI) (**A**) and sleep efficiency (**B**) in surface under the cumulative ranking curves (SUCRA).

Discussion

In the pairwise meta-analysis, the direct evidence based results showed that, among the 8 drugs including IMF, caffeine, montelukast, budesonide, fluticasone, pregabalin plus celecoxib, sucralfate and clindamycin, compared with placebo, the four drugs (IMF, montelukast, budesonide and fluticasone) showed better efficiency regarding AHI; fluticasone showed better efficiency regarding sleep efficiency; sucralfate and clindamycin showed better efficiency regarding VAS. IMF is a glucocorticosteroid used topically to reduce inflammation of the skin or in the airways, and can be applied as significant drug into the posterior nasal cavity.[28,29] Non-surgical treatment for childhood OSA is gaining popularity, a placebo-controlled trial demonstrated that IMF treatment effectively reduces the severity of mild OSA in children with significantly improved AHI and oxygen desaturation index, which is consist with our pairwise meta-analysis.[13] Montelukast is a leukotriene receptor antagonist for the maintenance treatment of asthma and relieving symptoms of seasonal allergies.[30,31] In addition, daily oral montelukast effectively reduces OSA severity and underlying adenoidal hypertrophy in children with non-severe OSA with one significant improvement in obstructive apnea index in a placebo-controlled study.[26] Efficiency of different therapeutics methods has been assessed, and montelukast treatment using leukotriene receptor antagonist administration has a good effect for mild OSAHS in children.[7] Sucralfate is a medication primarily taken to treat active duodenal ulcers, and shows improvement in the mucosal healing process, and beneficial effect of sucralfate has been found in reduction of oropharyngeal pain in postoperative adenotonsillectomy.[32,33] Clindamycin is an antibiotic for treating bacterial infections, and topical clindamycin was used as a beneficial method in reducing pain on the first postoperative day in post-adenotonsillectomy analgesia in children, and sucralfate and clindamycin are evidenced as safe drugs without obvious adverse effects in children with sleep apnea or snoring.[14,34]

Network meta-analysis results further confirmed that fluticasone regarding AHI is better than the following five drugs: placebo, IMF, caffeine, montelukast and budesonide; and budesonide shows better treatment effect regarding sleep efficiency when compared with placebo, fluticasone and montelukast in the treatment of OSAHS. Evidence has accumulated to suggest a significant role of non-surgical alternatives including drug treatment especially in children with OSAHS, and intranasal corticosteroids are potentially useful interventions for children suffering from OSA.[16,35] Corticosteroids suppress *in vitro* tonsillar proliferation in children suffering from OSA, and therapeutic effects of corticosteroids may lie in the management of lymphadenoid hypertrophy underlying the development of OSA in children.[36] Beneficial effects are observed in children with mild OSA receiving a combination of intranasal corticosteroid and oral montelukast as initial treatment, providing an effective alternative to adenotonsillectomy for children with OSAHS.[37] Fluticasone is a synthetic glucocorticoid, budesonide is a steroid medication, and both of them are considered as topical anti-inflammatories for the treatment of OSA in children.[16] Consistent with our results, nasal fluticasone may be potentially

useful intervention in ameliorating pediatric OSA characterized by decreased frequency of obstructive apnea and hypopnea;[27] reduction of interleukin-6 caused by fluticasone furoate, a synthetic corticosteroid derived from fluticasone, nasal spray treatment could contribute to the clinical efficacy of corticosteroids in the treatment of childhood OSAHS.[38] As previously reported, the administration of budesonide is associated with decreased snoring frequency and improved the polysomnography findings.[39] Similarly, administration of nasal budesonide has improved polysomnography findings and symptoms in children suffering from mild sleep-disordered breathing.[40] In addition, intranasal budesonide may be effective in reducing the severity of mild OSAHS and in the magnitude of adenoidal hypertrophy compared with placebo; so topical steroids can be used as the first-line choice for children suffering from mild OSA.[25] Caffeine administration is well-know in its acute sleep-suppressing effects; however, our study found that caffeine failed to achieve any better effects when comparing with placebo or any other drugs regarding AHI. Caffeine is the standard treatment for apnea of prematurity, and animal studies have suggested that neonatal caffeine administration can lead to permanent abnormalities in sleep regulation and ventilatory control.[41] Caffeine group had a longer total recording time and longer total sleep time in the caffeine group compared with the placebo group, although the sleep efficiency was similar.[18] Therefore, the caffeine may have certain effects on efficacy of OSAHS, which may need further confirmation in future.

Our network meta-analysis has several limitations: 1) The difference in sample size of the eight drug intervention and the difference in the number of the enrolled studies for direct pair comparison of different interventions may have a certain impact on the results of the study; 2) The number of included studies involved in AHI, sleep efficiency, VAS and types of intervention measures are unequal, which may also cause a certain impact on the overall results. These limitations might lead to a slight reduction in the validity of our overall results.

In conclusion, Bayesian network model to fit the direct evidence and indirect evidence in seven RCT studies and therapeutic effects of eight drugs on children with OSAHS has been assessed. The network meta-analysis clearly shows that fluticasone and budesonide have relatively good effects in the treatment of OSAHS in children, thus providing an important guiding significance for the treatment of OSAHS in children. However, because of the limitations in our study, our conclusion is needed to be confirmed by more adequately designed studies for future clinical applications.

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Ethical approval: It is a meta-analysis, ethical approval is not applicable.

Competing interest: There was no conflict of interest existing in this paper.

Contributors: Zhang J searched the literature, analyzed the data, and drafted the manuscript. Chen J searched the literature, and drafted the manuscript. Yin Y analyzed the data. Zhang H contributed to drafting the manuscript. All authors read and approved the final submitted manuscript.

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