REVIEW ARTICLE

Beyond CPAP in OSA

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Introduction

In the early days, the treatment of obstructive sleep apnea (OSA) was surgical therapy, by performing permanent tracheostomy, which could bypass the site of obstruction in the upper airway.[1] Since its description in 1981 by Sullivan and colleagues,[2] continuous positive airway pressure (CPAP) therapy, that could alleviate upper airway obstruction through air-pressure 'splinting' of collapsible upper airway segments, has become the treatment of choice for OSA. But, an alternative treatment may be required if CPAP is not feasible for medical or psychological reasons. Also, it has been shown that severely symptomatic patients with frequent apnea/hypoapnea readily improve with CPAP therapy, but in asymptomatic patients there is no measurable benefit and hence compliance with CPAP is much less in such patients.[3] There are a multitude of other treatment options for OSA, which can be broadly classified into conservative, apparative, pharmacological and surgical methods.

Conservative

Conservative methods include weight reduction, optimizing sleeping hygiene, conditioning in respect to the avoidance of certain sleep positions and medicinal treatments. Obesity constitutes a major risk factor for OSA[4] and several studies have shown that weight reduction significantly improves OSA in the short run, but the long-term success rate does not exceed 3%.[5] Weight loss has been shown to be associated with reduction of upper airway collapsibility and a fall in resistance to airflow in awake patients.[6,7] Although weight loss is important and can facilitate the treatment of OSA, it can rarely cure it without being associated to classical techniques, such as nasal CPAP.

The maintenance of a certain level of sleeping hygiene with sufficient and regular sleep hours, avoidance of alcohol and sedatives, reduction of nicotine and other noxious substances, observance of a regular sleep rhythm, etc. is part of the standard recommendations in the treatment of OSA. Obviously, no controlled long-term studies exist relating to these measures.

Oksenberg and co-workers reported that more than 50% of patients had posture-dependent OSA.[8] In the case of positional OSA, apneas and hypopneas occur predominantly or solely only in the supine position. In the supine posture, the tongue tends to fall back due to gravitational forces unless these forces are counteracted by enhanced activity of the genioglossus muscle, which pulls the tongue forward.[9] Patients may feel more comfortable sleeping in lateral position and a short-term therapy success of 75% has been documented in the case of mild and moderate positional OSA by using waistcoats that prevent a supine sleeping position.[10] Less severely affected patients would be more likely to respond to positional therapy, providing for a useful treatment option in the milder group of OSA patients who frequently are less tolerant of CPAP.

Apparative

Apparative treatment options include respiratory treatment with continuous positive airway pressure with its various modifications, oral appliances, and electrostimulation. There are three types of oral devices: the tongue-retaining devices, the mandibular advancement devices (MAD), and the soft palate lifters, which may be combined with tongue extensors. In the recent years, mandibular advancement appliances

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have had the most success. They have been proven to be the most effective treatment while at the same time entailing the fewest side effects. For mild to moderate OSA, success rates of 50–70% have been reported.[11-13] When fitted to the teeth these intra-oral devices reposition the mandible forward during sleep and increase the upper airway lumen by protrusion of the mandible and tongue,[14] increase the upper airway muscle tone,[15] and reduce the passive pharyngeal wall compliance.[16] They are shown to improve nocturnal breathing disturbances, symptoms, quality of life, vigilance and blood pressure in OSA patients.[17-19]

The oral appliances are easy to apply, handy, not dependent on electricity and are portable. Also, sleeping with an oral appliance is perceived as less socially disturbing than wearing a CPAP mask. These devices may be effective in controlling symptoms of OSA, nocturnal breathing disturbances, oxygenation and sleep disturbances, and even blood pressure. Although its efficacy in improving symptoms of OSA is reported to be as good as CPAP, in a few studies, but patients rate CPAP to be more effective than MAD but the latter to be more convenient. This may contribute to a higher treatment adherence with MAD.[20] In another study, MAD were shown to be effective even in severe cases of OSA. The higher the number of apnoea/hypopnoea, the greater was their reduction by MAD.[21] Subjective compliance of oral devices is reported to be 40–80%.[22,23] Unfortunately, individual success as well as compliance with MAD cannot be predicted. CPAP is efficacious in all patients but the intraoral devices are not. Its side effects are mild, but very common. The main side effects include hypersalivation, xerostomia, tooth movement, bite changes, temporomandibular joint pain and dental discomfort, which can be found in almost 80% of the patients.[24-26] Potential limitations of MAD are the requirement of a minimal number of stable teeth (ie, at least 8 teeth in the upper and lower jaw), absence of gingival disease and temporo-mandibular joint pain. Hence, the intraoral device may be used only as a second-line therapy and their long-term effectiveness and side effects require further study.

The guidelines from the American Academy of Sleep Medicine (AASM) Standards of Practice Committee have formulated the following indications of oral devices:[13,27]

1. For patients where sleep apnea has been ruled out and the major concern is the snoring.
2. For patients diagnosed with mild sleep apnea where weight loss and/or positional therapy is not an option.
3. For patients with moderate to severe sleep apnea who are intolerant of CPAP therapy or refuse this as a means of managing their sleep apnea.
4. For patients who have failed surgery, are not candidates for surgery, or refused surgery.

AASM have also published situations in which oral devices are not indicated for use.[13,27] They are:

1. In patients who are diagnosed with only central sleep apnea.
2. In patients who are compromised dentally.
3. In patients who have temporomandibular joint dysfunction or other types of oro-facial complaints.

In patients with OSA, respiratory activation of upper airway muscles, particularly genioglossus, is ineffective during sleep. It has been proposed that nocturnal electrical stimulation of the hypoglossal nerve by an implanted pace-maker may prevent sleep related upper airway collapse in such patients by activating submandibular muscles.[28-30] Currently, electrostimulation as standard procedure is available only for the transcutaneous or transcutaneous–transmucous application. Initial data from small case series display a short-term subjective success in the treatment of simple snoring but not for OSA. However, this treatment is still experimental and there is insufficient evidence to support its clinical use.[29,30]

Surgery

Surgery for obstructive sleep apnoea/hypopnoea syndrome aims to alleviate symptoms of daytime sleepiness, improve quality of life, and reduce the signs of sleep apnoea recorded by polysomnography. Surgery has two potential roles: first as an adjunct to nasal CPAP in individuals with nasal obstruction, and second, in patients who fail CPAP due to inability to use the therapy. Surgical procedures are performed both in the case of primary snoring and at all severity levels of OSA. The more severe the SDB, the more aggressive the surgical therapy required, if it is to be effective. For the treatment of primary snoring, minimally invasive techniques with a low complication rate should be preferred. In the case of higher level OSA, surgery is only secondarily indicated after an unsuccessful nasal CPAP therapy. For a primary surgical treatment, an apneoa/hypoapnoea index (AHI) of approximately 30 is considered as threshold value.[31]

Initially in the 1960s and 1970s tracheostomy was the only therapy available for OSA.[1] Tracheostomy bypasses the site of obstruction in the upper airway and should provide

a complete cure, but it has serious disadvantages including technical problems involved in performing tracheostomy in obese patients, postoperative complications like infection and dehiscence, and cosmetic disfigurement.

Nasal surgery rarely affects the severity of OSA and is of use only in the minority of patients with primary snoring. But it may be used as an adjuvant therapy especially to facilitate nasal ventilation therapy with CPAP. The success rate of only nasal surgery for OSA is low, less than 20%.[32] As nose is neither the site of obstruction during apneas nor the site of generation of snoring.

Surgeries proposed for treatment of OSA include Bypass upper airway Tracheotomy; Soft tissue ablation-Retropalatal Uvulopalatopharyngoplasty (UPPP), laser-assisted uvulopalatoplasty (LAUP), Retrolingual Laser midline glossectomy/lingualplasty (LMG), radiofrequency tongue base ablation (RFTBA), tongue base reduction with hyoepiglottoplasty (TBRHE), Retropalatal and Uvulopalatopharyngoglossoplasty (UPPGP); Skeletal modification Retropalatal Transpalatal advancement pharyngoplasty (TPAP), Retrolingual Mandibular advancement (MA), genioglossal advancement (GA), hyoid myotomy and suspension of hyoid from mandible, hyoid myotomy and attachment of hyoid to thyroid cartilage, Retropalatal and Maxillomandibular advancement (MMA).

UPPP is the most commonly performed surgery for OSA. It was introduced in 1981 by Fujita as a procedure which avoided the necessity of neck opening by amputating the uvula, excising the tonsils, and tightening the pharyngeal mucosa, thereby widening the pharyngeal cross section.[33] However, it was soon realized that a large percent of subjects with OSA had their site of narrowing or obstruction at the level of the base of the tongue at a distance from the site of the UPPP and the procedure could cause only 50% reduction in AHI.[34] In a large meta-analysis, the success rate of UPPP for OSA has been estimated at about 40.7%.[35]

Tongue base procedures including suspension or resection have been performed for management of OSA. But, these procedures have been performed in small patient groups and the results require further confirmation.[36] Tracheotomy and maxillo-facial surgery are aggressive procedures and are not recommended routinely.

OSA is increasingly considered as a disorder of the entire upper airway. In an attempt to achieve the maximum degree of improvement in each individual patient while minimizing the extensiveness of surgical intervention, protocols have been established by which surgery is staged in planned sequential phases. The Stanford step-by-step approach for surgery in OSA is considered in patients not successfully treated with CPAP.[37,38] The first stage comprises limited mandibular osteotomy (with or without UPPP, genioglossus advancement, hyoid myotomy, and hyothyroidopexy). Maxillo-mandibular advancement osteotomy, stage II surgery, is considered if stage I is not successful, or in the first place if cranio-facial dysmorphia is present.[39]

One of the main reasons for OSA in children is tonsillar hypertrophy[40] and children with severe OSA show reduced neurocognitive performance, which is reversible after combined adenotonsillectomy.[41] An isolated adenoidectomy does not seem to be as effective as an isolated tonsillectomy nor as a combined adenotonsillectomy.[42] The cure rate of adenotonsillectomy as an isolated procedure in children is approximately 85–95%.[43-45] As substantial hypertrophy of the palatine tonsils is rare in adults, adenotonsillectomy does not have any significant role in adults with OSA but in selected patients including those with adeno-tonsillar hypertrophy, and cranio-facial malformations various surgical techniques that enlarge the upper airway may be a treatment option for OSA.[46]

In morbidly obese patients suffering from OSA bariatric surgery should be considered as a treatment that reduces obesity and at the same time improves OSA. Gastric surgery may allow marked loss in weight, which may be associated with significant improvements in parameters of sleep-disordered breathing, sleep architecture and quality of sleep, and severity of obesity-related diseases such as diabetes and hypertension. Marked reductions in AHI and improvement in oxygen saturation has been reported after gastric surgery in obese patients.[47]

There are a few trials assessing different surgical techniques with inactive and active control treatments. The studies assembled do not provide evidence to support the use of surgery as primary treatment of sleep apnoea/hypopnoea syndrome, as overall significant benefit has not been demonstrated.[48]

Pharmacological Therapy

Though, drug therapy has been proposed as an alternative to CPAP in some patients with mild to moderate sleep apnoea and could be of value in patients intolerant of CPAP, unfortunately there are currently no drugs that allow effective pharmacological therapy of OSA. These include an increase in tone in the upper airway dilator muscles, an increase in ventilatory drive, a reduction in the proportion

of REM sleep, an increase in cholinergic tone during sleep, a reduction in airway resistance and a reduction in surface tension in the upper airway. Many agents have been used so far, including alkaloids and analeptics, which also stimulate the pharynx musculature via the respiratory center, tricyclic antidepressants, which reduce the portion of REM sleep, antihypertensives, methylxanthines, oxygen, progesterone analogs, and others.[49] In compliant OSA patients with residual hypersomonolence despite exclusion of other causes and effective CPAP treatment, modafinil, a drug prescribed to treat hypersomnolence in narcoleptics, has been used as an adjunct to improve alertness.[50] No reports exist of patients with polysomnographic data who have received therapy for more than 18 months. Even for theophylline, a methylxanthine frequently used in Germany, there are no long-term results.[49] Presently, there is insufficient evidence to recommend the use of drug therapy in the treatment of OSA. Small studies have reported positive effects of certain agents based on short-term outcome. Individual patients had more complete responses to particular drugs and it is likely that better matching of drugs to patients according to the dominant mechanism of their OSA will lead to better results but this also needs further study.[51]

Conclusion

CPAP therapy is the most successful treatment modality available for management of OSA but its efficacy is compromised because a large proportion of patients cannot tolerate or are non-adherent to its regular use. Life style changes, weight reduction and sleeping in lateral position may improve symptoms in mild OSA and should be a part of the standard recommendations in the treatment of OSA. Removable oral appliances are attractive and acceptable treatment option for patients with OSA not able or not willing to tolerate the standard CPAP therapy. Although newer surgical procedures are also available to treat OSA and experimental approaches to treatment, such as electrical stimulation of pharyngeal dilator muscles are under development, positive airway pressure therapy is likely to remain the mainstay of therapy well into the future.

References

1. **Coccagna G**, Mantovani M, Brignani F, Parchi C, et. al. Tracheostomy in hypersomnia with periodic breathing. *Bull Physiopathol Respir (Nancy) 1972; 8: 1217–1227.*
2. **Sullivan CE**, Berthon-Jones M, Issa FG, Eves L. Reversal of obstructive sleep apnea by continuous positive airway pressure applied through the nares. *Lancet 1981; 1: 862–5.*
3. **Barbe F**, Mayoralas LR, Duran J, Masa JF, Maimo A, Montserrat JM, et. al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. A randomized, controlled trial. *Ann Intern Med 2001; 134: 1015–23.*
4. **Browman CP,** Sampson MG, Yolles FS, Gujavarti KS, Weiler SJ, Walsleben JA, Hahn PM, Mitler MM. Obstructive sleep apnea and body weight. *Chest 1984; 85: 435–438.*
5. **Sampol G**, Munoz X, Sagalés MT, Marti S, Roca A, Dolors de la Calzada M, Lloberes P, Morell F. Long-term efficacy of dietary weight loss in sleep apnoea/hypopnoea syndrome. *Eur Respir J 1998; 12: 1156–1159.*
6. **Schwartz AR**, Gold AR, Schubert N, Stryzak A, et. al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis 1991; 144: 494–498.*
7. **Hakala K**, Maasilta P, Sovijarvi AR. Upright body position and weight loss improve respiratory mechanics and daytime oxygenation in obese patients with obstructive sleep apnoea. *Clin Physiol 2000; 20: 50–55.*
8. **Oksenberg A**, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: Anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest 1997; 112: 629–639.*
9. **Malhotra A**, Fogel R, Stanchina M, Patel SR, et. al. Postural effects on pharyngeal protective reflex mechanisms. *Sleep 2004; 27: 1105–1112.*
10. **Maurer JT**, Hein G, Stuck BA, Verse T, Hörmann K. Treatment of obstructive sleep apnea with a new vest preventing the supine position [in German]. *DMW 2003; 128: 71–75.*
11. **Marklund M**, Franklin KA, Sahlin C, Lundgren R. The effect of a mandibular advancement device on apneas and sleep in patients with obstructive sleep apnea. *Chest 1998; 113: 707–713.*
12. **Menn SJ,** Loube DI, Morgan TD, Mitler MM, Berger JS, Erman MK. The mandibula repositioning device: Role in the treatment of obstructive sleep apnea. *Sleep 1996; 19: 794–800.*
13. **Schmidt-Nowara W**, Lowe A, Wiegand L, Cartwright R, Perez-Guerra F, Menn S. Oral appliances for the treatment of snoring and obstructive sleep apnea: a review. *Sleep 1995; 18: 501–510.*
14. **Ferguson KA**, Love LL, Ryan CF. Effect of mandibular and tongue protrusion on upper airway size during wakefulness. *Am J Respir Crit Care Med 1997; 155: 1748–54.*
15. **Yoshida K**. Effect of a prosthetic appliance for treatment of sleep apnea syndrome on masticatory and tongue muscle activity. *J Prosthet Dent 1998; 79: 537–44.*
16. **Kato J,** Isono S, Tanaka A, Watanabe T, Araki D, Tanzawa H, et. al. Dose-dependent effects of mandibular advancement on pharyngeal mechanics and nocturnal oxygenation in patients with sleep-disordered breathing. *Chest 2000; 117: 1065–72.*
17. **Bloch KE**, Iseli A, Zhang JN, Xie X, Stoeckli PW, Russi EW.

Randomized controlled trial of two oral appliances for sleep apnea treatment. *Am J Respir Crit Care Med 2000; 162: 246–51.*

18. **Gotsopoulos H**, Chen C, Qian J, Cistulli PA. Oral appliance therapy improves symptoms in obstructive sleep apnea: A randomized controlled trial. *Am J Respir Crit Care Med 2002; 166: 743–8.*
19. **Gotsopoulos H**, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnea: A randomized controlled trial. *Sleep 2004; 27: 934–41.*
20. **Barnes M**, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, et. al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. *Am J Respir Crit Care Med 2004; 170: 656–64.*
21. **Henke KG**, Frantz DE, Kuna ST. An oral elastic mandibular advancement device for obstructive sleep apnea. *Am J Respir Crit Care Med 2000; 161: 420–5.*
22. **Ferguson KA**, Ono T, Lowe AA, Keenan SP, Fleetham JA. A randomized crossover study of an oral appliance vs nasal-continuous positive airway pressure in the treatment of mild-moderate obstructive sleep apnea. *Chest 1996; 109: 1269–1275.*
23. **Clark GT**, Blumenfeld I, Yoffe N, Peled E, Lavie P. A crossover study comparing the efficacy of continuous positive airway pressure with anterior mandibular positioning devices on patients with obstructive sleep apnea. *Chest 1996; 109: 1477–1483.*
24. **Fritsch K**, Iseli A, Russi EW, Bloch KE. Side effects of mandibular advancement devices for sleep apnea treatment. *Am J Respir Crit Care Med 2001; 164: 813–8.*
25. **Fransoon A**, Tegelberg A, Svenson X, Lennartsson B, Isacsson G. Influence of mandibular protruding device on airway passages and dentofacial characteristics in obstructive sleep apnea and snoring. *Am J Orthod Dentofacial Orthop 2002; 22: 371–379.*
26. **Pantin CC,** Hillman DR, Tennant M. Dental side effects of an oral device to treat snoring and obstructive sleep apnea. *Sleep 1999; 22: 237–240.*
27. **Schmidt-Nowara W**, Lowe A, Wiegand L, Cartwright R, Perez-Guerra F, Menn S. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances. *Sleep 1995; 18: 511–513.*
28. **Schwartz AR**, Bennett ML, Smith PL, De Backer W, Hedner J, Boudewyns A, et. al. Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg 2001; 127: 1216–23.*
29. **Randerath WJ,** Galetke W, Domanski U, Weitkunat R, Ruhle KH. Tongue-muscle training by intraoral electrical neurostimulation in patients with obstructive sleep apnea. *Sleep 2004; 27: 254–259.*
30. **Verse T**, Schwalb J, Hörmann K, Stuck BA, Maurer JT. Submental transcutaneous electrical stimulation for obstructive sleep apnea [in German]. *HNO 2003; 51: 966–970.*
31. **Pirsig W**, Hörmann K, Siegert R, Maurer J, Verse T. Leitlinie der Deutschen Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Halschirurgie „Obstruktive Schlafapnoe" [in German]. *HNO 1998; 46: 730.* Guideline of the German society for Neck nose ear medicine, head and neck surgery "obstructive sleep apnea"
32. **Hoffstein V**, Mateika S, Metes A. Effect of nasal dilation on snoring and apneas during different stages of sleep. *Sleep 1993; 16: 360–365.*
33. **Fujita S**. Surgical correction of anatomic abnormalities in obstructive sleep apnea syndrome: Uvulopalatopharyngoplasty. *Otolaryngol Head Neck Surg 1981; 89: 923–934.*
34. **Walker-Engstrom ML**, Tegelberg A, Wilhelmsson B, Ringqvist I. 4-year follow-up of treatment with dental appliance or uvulopalatopharyngoplasty in patients with obstructive sleep apnea: A randomized study. *Chest 2002; 121: 739–746.*
35. **Sher AE**, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep 1996; 19: 156–177.*
36. **Thomas AJ,** Chavoya M, Terris DJ. Preliminary findings from a prospective, randomized trial of two tongue-base surgeries for sleep-disordered breathing. *Otolaryngol Head Neck Surg 2003; 129: 539–46.*
37. **Powell N**. Upper airway surgery does have a major role in the treatment of obstrucive sleep apnea. "The tail end of the dog". *J Clin Sleep Med 2005; 1: 236–40.*
38. **Riley RW,** Powell NB, Guilleminault C. Obstructive sleep apnea syndrome: A review of 306 consecutively treated surgical patients. *Otoloaryngol Head Neck Surg 1993; 108: 117–25.*
39. **Bettega G,** Pepin JL, Veale D, Deschaux C, Raphael B, Levy P. Obstructive sleep apnea syndrome: Fifty-one consecutive patients treated by maxillofacial surgery. *Am J Respir Crit Care Med 2000; 162: 641–9.*
40. **Guilleminault C**, Eldridge FL, Simmons FB, Dement WC. Sleep apnea in eight children. *Pedriatrics 1976; 58: 23–30.*
41. **Friedman BC**, Hendeles-Amitai A, Kozminsky E, Leiberman A, Friger M,Tarasiuk A, Tal A. Adenotonsillectomy improves neurocognitive function in children with obstructive sleep apnea syndrome. *Sleep 2003; 26: 999–1005.*
42. **Nieminen P,** Tolonen U, Löppönen H. Snoring and obstructive sleep apnea in children. A 6-month follow-up study. *Arch Otolaryngol Head Neck Surg 2000; 126: 481–486.*
43. **Brodsky L**, Adler E, Stanievich JF. Naso- and oropharyngeal dimensions in children with obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol 1989; 17: 1–11.*
44. **Ahlquist-Rastad J**, Hultcrantz E, Svanholm H. Children with tonsillar obstruction: Indications for and efficacy of tonsillectomy. *Acta Pediatr Scand 1988; 77: 831–835.*
45. **Laurikainen E**, Aitasalo K, Erkinjuntti M, Wanne O. Sleep apnea syndrome in children – secondary to adenotonsillar hypertrophy. *Acta Otolaryngol 1992; Suppl 492: 38–41.*
46. **Houghton DJ,** Camilleri AE, Stone P. Adult obstructive sleep apnoea syndrome and tonsillectomy. *J Laryngol Otol 1997;*

111: 829–832.

47. **Charuzi I**, Ovnat A, Peiser J, Saltz H, et. al. The effect of surgical weight reduction on sleep quality in obesity-related sleep apnea syndrome. *Surgery 1985; 97: 535–538.*

48. **Sundaram S**, Bridgman SA, Lim J, Lasserson TJ. Surgery for obstructive sleep apnoea. *Cochrane Database Syst Rev 2005 Oct 19; (4): CD001004.*

49. **Hein H**, Magnussen H. Who did what with drugs in sleep apnea syndrome? [in German] *Somnologie 1998; 2: 77–88.*

50. **Kingshott RN**, Vennelle M, Coleman EL, Engleman HM, Mackay TW, Douglas NJ. Randomized, double-blind, placebo controlled crossover trial of modafinil in the treatment of residual excessive daytime sleepiness in the sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med 2001; 163: 918–23.*

51. **Smith I**, Lasserson TJ, Wright J. Drug therapy for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev 2006 Apr 19; (2): CD003002.*