Review Article

Complications and safe prescription of interventions for adult sleep disordered breathing in Australia

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Abstract: The American Academy of Sleep Medicine (AASM) identifies continuous positive airway pressure (CPAP), mandibular advancement splint (MAS), adjunctive medical therapy and surgical modifications of the upper airway potential treatment modalities in adult sleep breathing disorders and promotes a number of Guidelines and Consensus Statements to outline the role of such therapies. Specific treatments under each of these "intervention guidelines" are highlighted as standard, option or guideline with stringent literature analyses supporting each—by derivation, treating clinicians in relevant sleep disciplines should be highly trained and credentialed. Unfortunately, in Australia and elsewhere, sleep disorders, including sleep disordered breathing (SDB), are increasingly being managed by those without the necessary training or expertise, and "pop up" sleep clinics are bypassing comprehensive clinician assessment. This Symposium-derived paper highlights the risks and technical considerations related to each category of available intervention. This paper represents the first time such a focus has been published and incorporates CPAP, MAS, medical therapy and surgery in the same document. This paper explores in detail the complications associated with each of the interventions, and emphasises the requirement for meticulous training and experience to predict, identify, manage and resolve all relevant occurrences. The paper is a summation and expansion of proceedings from the Opening Plenary of the Australasian Sleep Association Scientific Conference from October 2017, and features the four key presentations of Professor Matthew Naughton, Professor Peter Cistulli, Associate Professor Nigel McArdle and Professor Stuart MacKay.

Keywords: Obstructive sleep apnoea (OSA); OSA guideline; continuous positive airway pressure (CPAP); mandibular advancement splint (MAS); sleep medicine; sedative hypnotics; wakefulness promoters; sleep surgery

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How safe is continuous positive airway pressure (CPAP)?

Guidelines and Consensus Statements outline the role of specific therapies for obstructive sleep apnoea (OSA) (1-3). The landmark paper by Sullivan *et al.* (4) in 1981 permitted a straightforward approach to treating OSA with CPAP. Debate did follow, some agreeing (5) and others criticising social, technical and physiologic problems encountered with initial and long-term use of CPAP (6).

A degree of scepticism developed about the complexity of dealing with pumps, masks and pressures in real life

Table 1 Complications of continuous positive airway pressure (CPAP)

Medical	Mechanical
Hypotension/preload	Safety (electrical)
Nasal bridge skin ulceration	Education
Aerophagia	Masks
Conjunctivitis	Tubing
Xerostomia	Humidification
Infection	Cleanliness
Rhinosinusitis	Pressure settings
Epistaxis	Output: apnoea/hypopnoea index analysis
Pneumocephalus/ barotrauma	Upselling
Anxiety/claustrophobia	Medicolegal
Craniofacial distortion	Diagnosis correct/incorrect

clinical practice. Human physiology does not always follow engineering principles of "if in doubt, pressurise the snout", illustrated with the Servo-ventilation Heart Failure Trial (7) dealing with heart failure in central sleep apnoea.

Sleep disordered breathing (SDB) is complex and the application of CPAP does not offer a ubiquitous solution. In addition to adherence rates as low as 30% (8), CPAP therapy carries an up to 70% complication rate for those utilizing it (9). Such complications can be divided into medical and mechanical (*Table 1*).

CPAP at high pressures can impede venous return to the heart, even in healthy individuals, leading to decreased cardiac output (10). There are potential cardiac and pulmonary side effects in patients with or without pre-existing heart problems.

Nasal complications such as epistaxis (11) and rhinitis (12) are relatively common. Ulceration as a result of CPAP across the nasal bridge (13) can cause skin necrosis and infection, potentially leading to peri-orbital cellulitis and intracranial complications. Aerophagia to the extent of intense small and large bowel trapping has been documented (14).

Pneumocephalus from CPAP use following skull base surgery has occurred (15) and this risk applies following skull base fracture (16).

Complex patients requiring CPAP, such as those with previous head and neck tumour resection, prior airway surgery (including resective uvulopalatopharyngoplasty) or with underlying syndromes may have difficulty with tolerance due to anatomic and functional changes in the upper airway.

Mental health issues and a relationship between OSA and anxiety/depression (17-19) indicate that treating OSA with CPAP can improve sleepiness and Hospital Anxiety Scores (HADS), but untreated depression may reduce acceptance of CPAP (20) if treated without trained professional expertise.

Respiratory infection on humidified CPAP has been reported, both upper respiratory tract infections (21) and lower (22), the latter in a large cohort of 34,000 patients. CPAP was a risk factor for the spread of SARS (23) and other viral outbreaks (24,25). Positive airway pressure carries the risk of expelling organisms into the atmosphere and may place health care workers at risk.

Craniofacial changes can occur with CPAP. A Japanese study utilising lateral cephalograms at baseline and again at two years of CPAP use, identified bony changes (26), such as maxillary retrusion, setback supramentale and maxillary incisor retro-inclination even when patients are not aware of changes.

Medico-legal responsibility when patients are involved, for example, in motor vehicle accidents, lies with dedicated trained sleep professionals, but it is not clear what level of responsibility lies with "pop-up clinics" who administer CPAP.

On the industry side of things, early CPAP devices caused a metallic accumulation between the internal CPAP motor and metal casing with consequent electrocution. Fires from faulty CPAP transformers have been reported (27).

Training of staff who administer CPAP is an important issue, for example, understanding vented and non-vented masks and optimising tubing orientation and directionality are critical. Case examples of death following inappropriate or lack of adequate non-invasive ventilation in hospital patients with severe cardiopulmonary failure in Australia have been reported to the coroner (28).

Industry integrity and training can be problematic. The sale of old or inappropriate machines or masks occurs. Clear pathways defining industry engagement in repair provisions should be considered. Residual apnoea on downloads requires medical review, not industry upsell.

Financial costs can be limiting for some patients, such as electricity costs which range between $10–$100 per year to utilise CPAP, depending upon device type and peak and off-peak usage. Moreover, power failure during CPAP use as a cause of death has been reported (29).

The SAVE trial demonstrated a 0.1% serious adverse event rate with patients using CPAP, and a 36% adverse event rate for those that withdrew from regular use (19). In the APPLES trial, a 40% side effect rate was noted (30) although whether these effects were CPAP-related or not is unknown. Thus, adverse effects related to the device, whether real or simply perceived, are commonplace.

Overall, CPAP is safe, but only with a strong awareness of possible complications. Most side effects are medical, manufacture or patient-related. Education is critical. CPAP in Australia should be prescription only, and this potentially should be mandated worldwide, as it is in USA, Israel, Hong Kong, Ireland, Italy, UK and Canada. The critical requirement is for a trained clinician to take responsibility over treatment.

Mandibular advancement splints (MASs): think before sinking your teeth into oral appliance (OA) therapy

MASs or OAs have been used in OSA treatment for 30 years (31), but have only gained acceptance as a clinical therapy in the last 10 years. These intra-oral devices to improve airway function come in many different designs with the majority retained on the teeth to advance the mandible forward to improve airway dimensions.

The first systematic evaluation of side-effects of MAS use was performed in Perth and published in 1999 (32). One hundred and seven of 132 patients over five years reported side-effects, and 10 discontinued use. Side effects included excessive salivation (40 patients), xerostomia (30 patients), temporomandibular joint dysfunction (TMJ) (35 patients), dental discomfort (35 patients), myofascial discomfort (33 patients) and bite changes (16 patients).

Similar symptoms were reported in a larger Canadian study (33) of 544 patients who were surveyed at a mean of 5.7 years. Thirty-six percent discontinued MAS use due to discomfort, perceived minimal effect or desire to switch to CPAP.

More recently, in 2015, a joint report of the American Academy of Sleep Medicine (AASM) and the American Dental Academy (ADA) highlighted some comments related to the MAS side-effects (34,35).

(I) There is a paucity of high-quality evidence relating to dental side-effects and adherence to oral therapy;
(II) There is a lack of studies describing strategies to mitigate OA side effects;
(III) There are few studies looking at comparing OA designs to see how they might influence side effects.

However, the report noted discontinuation of OA therapy to be about half that of CPAP therapy. Following this, the American Academy of Dental Sleep Medicine (AADSM) formed a committee that subdivided MAS complications into six key categories (*Table 2*).

TMJ related side-effects include morning pain, persistent pain, joint sounds and tenderness in muscles of mastication. However, OA may have a therapeutic effect on TMJ dysfunction in some patients (36-40). Specific exercises may also be of benefit in the initial stages of therapy (41).

Intra-oral side-effects are the result of a foreign body in the mouth, and include soft tissue and tongue irritation, gingival irritation, excessive salivation and drooling, and a dry mouth. The majority of these are minor and transient, mostly confined to the first few weeks of therapy acclimatisation (42,43).

Changes in occlusion concern the patient, the prescriber and the provider the most. These include altered occlusal contacts, decreased overjet and overbite, incisor changes, mesial shift of mandibular canines and molars and inter-proximal gaps in teeth. Lower teeth may move forward to sit in front of, or in an edge-to-edge relationship with the upper teeth. Overbite and overjet changes over many years have been noted relative to time (44). Most changes are subclinical and the patient is unaware: only 1–14% will be aware of tooth movement (32,45), but 86% will have examination findings of significance (46). Informed consent that details these risks at therapy onset is extremely important. In the worst cases, time-consuming and expensive orthodontic correction of complications are needed, or maxillomandibular advancement surgery is necessary. However not all tooth movement is "bad", and conversely, up to 41% of changes may be favourable (46).

The ORCADES study also showed that the risk/benefit profile is reasonably favourable and that major side-effects are not common (47).

Whilst MAS design features have not been investigated extensively, a rigid device with incisal coverage may cause less tooth irregularity over time when compared with a flexible device (48).

Prevention and prediction strategies largely relate to the use of *Morning Occlusal Guides* (gadgets to bite into in the morning in an attempt to return bite to normal), jaw exercises (which may also be beneficial in TMJ symptom reduction) (41), and use of conservative titration in preference to maximising advancement- the so called "sweet

Table 2 Complications of mandibular advancement splint (MAS) from the American Academy of Dental Sleep Medicine (AADSM) 2015

Temporomandibular joint changes	Intra-oral issues
Damaged teeth or restorations	Occlusal changes
Cephalometric changes	Appliance issues

spot" (49-51).

Appliance issues are related to breakage, allergy/irritation (52), gagging/choking or difficulty breathing (53). Some patients are subject to a sense of suffocation (33,53) causing therapy discontinuation.

Overall MAS/OA is an effective therapy, but side-effects are common, albeit minor. Trained sleep professionals with a good understanding of indications for therapy and well informed, consented patients as well as highly trained dentists are essential. Concern about "over-the-counter" or "self-administered therapy" are imminent and likely to create a huge volume of problems.

On the horizon, 3D digital imaging may come into play in detecting changes in dental position over years of therapy.

Adjunctive medications used in OSA treatment: how safe are they?

Three main types of adjunctive medications are used in OSA, usually to assist adaptation to primary physical therapies or to treat symptoms uncontrolled by primary therapies: (I) medications for nasal symptoms; (II) sedative hypnotics; (III) wake promoting agents.

Medications for nasal symptoms

The AASM has described intranasal corticosteroids (INCS) as "potentially useful adjuncts to primary therapies" (54). A randomized controlled trial (RCT) in the setting of OSA and co-existent rhinitis showed modest reduction in apnea-hypopnea index (AHI) (5.6 events per hour) compared to placebo (55). More commonly, INCS are used to treat nasal symptoms associated with CPAP use. A recent meta-analysis of 144 unselected OSA patients demonstrated use of INCS resulted in a non-significant trend to reduction in nasal symptoms (56). Additionally, CPAP use increased by 25 minutes, but this did not reach statistical significance.

INCS adverse reactions are usually local: irritation, dryness and burning/stinging, but these are similar in occurrence to placebo. Epistaxis is almost three times more frequent with INCS use than placebo (RR-2.74), but is usually mild and transient (57). Long-term biopsy studies have not shown increased risk of nasal mucosal atrophy, ulceration or septal perforation, although post-marketing data has demonstrated rare cases (58). Good nasal spray technique, such as pointing the nozzle away from the nasal septum, may minimise these local reactions (58).

INCS have low systemic bio-availability and thereby low risk of systemic adverse effects (for example, fluticasone propionate <1%, fluticasone furoate 0.5%, mometasone furoate <0.1%) (58), due to their high lipid solubility and high first pass liver metabolism. Consistent with the low bioavailability of these agents, studies have found no evidence of hypothalamic-pituitary axis damage, reductions in bone density or eye complications, such as cataracts (59). So, INCS can modestly improve OSA in concurrent rhinitis, and possibly act as an adjunct to facilitate CPAP use. INCS are well tolerated, with very low risk of serious adverse events and attention to technique is recommended.

Sedative hypnotics

Non-benzodiazepine hypnotics: zolpidem 5, 10 mg, zopiclone 7.5 mg, ezopiclone 1, 3 mg.

These are otherwise known as the "Z-drugs". Both the benzodiazepine and non-benzodiazepine drugs act on the neurotransmitter gamma-aminobutyric acid (GABA) receptors throughout the central nervous system. However, the "Z-drugs" are more specific for the alpha-1 subunit mediating sleep, and hence the theory is that they have lower central adverse events. There are very few studies, however, directly comparing benzodiazepine to non-benzodiazepine drugs for adverse events.

These drugs are considered "adjunctive" in that there are studies demonstrating that they may improve CPAP use. Eszopiclone used on a titration night results in better titration (according to several polysomnographic measures, such as sleep efficiency on the titration night). Nightly CPAP use was 54 minutes/night greater in the group that received ezopiclone on the titration night, as assessed after four weeks of CPAP use (60). In another study, a two-week course of ezopiclone increased CPAP use by 1.3 hours at 6 months compared to placebo (61).

A recent Cochrane review evaluating safety in OSA (62) showed no difference in the AHI or overnight oxygenation between the medication and placebo. This means that this group of drugs does not appear to worsen SDB.

The "Z-drugs" have also been postulated as a primary treatment modality in some patients with OSA and a low arousal threshold. In a study by Eckert *et al.* (63), Zopiclone was seen to reduce AHI. The authors measured arousal threshold using an epiglottic pressure catheter and found that those with the greatest reduction in AHI had low arousal thresholds. They excluded patients with severe disease, defined by a nadir oxygen saturation of <70%. Those people with severe disease usually had a high arousal threshold, so are most at risk for deleterious reactions to sedatives, yet they were not included in this or other studies.

In another study evaluating the effect of zolpidem on AHI, supratherapeutic doses lowered oxygen saturations (minimum oxygen saturation: 76.8% in active agent group *vs.* 85.2% with placebo, P value =0.02), but there was no difference in AHI (64). In a study assessing patients with severe OSA (defined as AHI >30), there was no difference in oxygen saturations or AHI during CPAP treatment compared to placebo (65). The Cochrane review authors note limitations in study design (62). The studies were relatively short-term (active agent for one night or two consecutive nights) and the confidence intervals were wide, meaning that these agents could increase the AHI.

In the insomnia literature, the "Z-drugs" are reportedly reasonably well tolerated, with low side effect rates of <5–10%, the most common of which is an unpleasant taste. Gastro-intestinal discomfort, headaches, somnolence and dizziness are also reported (66).

Serious adverse effects are uncommon. For example, the large (n=788) 6-month study by Krystal and colleagues (67) had a serious adverse event rate of 2.9% (compared to placebo =1%). Most of these were unrelated to the drug. Adverse events picked up in the post-marketing data also highlight central nervous system effects such as worsening depression, neurocognitive changes, delirium and confusion (68-70). While RCTs exclude those with certain medical conditions such as psychiatric conditions, post-marketing data would suggest that those with psychiatric conditions see a Psychiatrist before starting medication.

There has been some media attention on neuropsychiatric side effects from the "Z-drugs", such as delirium, confusion, sleep walking and even sleep driving, and it is important to be aware of the risk factors for these reactions. Increasing the dose increases the risk, as does female gender and older age (70).

Residual or 'hangover' effects can potentially influence function in high risk activities such as driving the day after bedtime use. Product information warns of this possibility and not to drive or operate dangerous machinery until it is known that they do not become drowsy after therapy (71). The risks of hangover effects are related to drug factors, such as dose and half-life and patient characteristics with extra care needed in the elderly, females and those on multiple medications, especially other psychoactive drugs (72).

As an example of post-marketing data picking up events not identified in the RCTs, an observational study using health administration data found that use of zolpidem in the elderly was associated with a doubling of the risk of hip fracture after controlling for confounding factors (73). In elderly patients, it is recommended to use the 5 mg zolpidem dose rather than 10 mg (70).

Non-amphetamine wake promoting agents

Modafinil and armodafinil

For some patients with clinically relevant sleepiness despite seemingly good CPAP use, the American Sleep Academy recommends Modafinil (74) (providing other identifiable causes of sleepiness have been excluded). Armodafinil has also been approved for this indication by the Australian Therapeutic Goods Administration (TGA) and the Food and Drug Administration (FDA).

Recent meta-analyses of RCTs for this indication, such as Chapman *et al.* (75) who reviewed trial data on 1,466 patients, confirmed a modest improvement in sleepiness subjectively (Epworth sleepiness score reduced by 2.2 points over placebo) and objectively (Maintenance of Wakefulness Test improved by 3 minutes over placebo). However, there was a higher rate of adverse events in the active agents with a 1.65 relative risk. The commonest adverse event was headache at 14% per patient year, compared with placebo at 7%. Other events were less than or equal to 5% per patient year and included nausea, anxiety, insomnia, diarrhoea and dizziness. The number of serious adverse events was small (not significantly different between active and placebo groups) and there were no deaths. Small rises in systolic (3 mmHg) and diastolic (1.9 mmHg) blood pressure were not thought to be clinically relevant. A major limitation of the meta-analysis was a lack of long-term safety data because the trials were not longer than three months.

A large (n=328) 12-month open label study of armodafinil (76) demonstrated systolic and diastolic blood pressure rises <1 mmHg. There were no clinically significant increases in heart rate and few patients had clinically significant electrocardiogram (ECG) changes. Of 15 serious adverse events, four possibly were related to

Table 3 Factors contributing to complications in obstructive sleep apnoea (OSA) surgery

Extent of operation	Surgical technique
Surgeon's experience	Anatomical/airway factors
General anaesthetic considerations	OSA severity
Patient age and co-morbidities	Peri-operative care

the drug and included nonspecific chest pain, pulmonary embolism, myocardial infarction and exacerbation of depression. The product information for armodafinil (77) notes that in the clinical studies there were three patients with underlying heart conditions, for example mitral valve prolapse and left ventricular hypertrophy, who developed signs such as palpitations or ECG changes. Post-marketing data indicate that psychiatric adverse reactions can occur, often in those with a prior history of psychiatric disease. It is recommended that caution be exercised in those with known cardiac or psychiatric disease.

There is no evidence from RCTs that polysomnographic sleep architecture is affected, but a concern is that CPAP may not be utilised as much. However, in a 12-week RCT by Roth *et al.* (78) there was a small reduction in CPAP use of 12 minutes when using Armodafinil compared to placebo, which is statistically significant but probably of no clinical relevance.

The potential for abuse of these drugs is thought to be relatively low (77,79) but euphoric effects can occur and may be a reason for abuse (79). Care should be taken in patients with a history of drug abuse and an awareness of drug-seeking behaviour is advised (77). Drug interactions can occur, including cytochrome P450 induction, rendering oral contraceptive pills ineffective. Barrier contraceptive methods are recommended as this medication is contraindicated in pregnancy. Barrier or other methods need to be continued for a month after stopping the medication (80).

Post marketing data has revealed rare but potentially life-threatening rashes, including Stevens-Johnson Syndrome, that occur above the background rate of these conditions in the population (77).

These drugs are associated with modest improvements in those with residual sleepiness on CPAP, they are generally well tolerated, but caution is needed with cardiovascular and psychiatric conditions, and rare and potentially life-threatening reactions can occur.

In conclusion, adjunctive medications can improve outcomes in subgroups of patients with OSA but careful patient selection and close supervision are needed because serious adverse effects can occur. A medical model is recommended for the safe use of adjunctive medications and those seeking OSA treatment outside this model (for example, those going directly to a pharmacy) are likely to miss out on the benefits of these medications.

Complications of surgery

Factors contributing to complications in OSA surgery are broadly outlined in *Table 3*. Contemporary airway surgery encompasses a broad range of procedures, reflecting heterogeneity in patient anatomy, in the disease, and in experience of the surgical team.

Anatomical heterogeneity makes the art of patient selection for surgery difficult, and the interpretation of the science of the literature vexed. Most publications in surgery look only at single level surgery, rather than multi-level, which is more reflective of real-life surgery. However, a large cohort study on 3,000 patients by Kezirian *et al.* (81) noted that surgeries involving multiple levels trended towards increased rate of significant complication. The concept is that the more we do to the patient, the more risk is conferred. Three main risk factors for complications were identified in the study. Increased body mass index (BMI), OSA severity (in that study, denoted by higher AHI) and co-morbid disease. Other factors to consider are age and bleeding dyscrasias. The numbers in that study were too small to demonstrate whether the effect of these individual risk factors was additive, but the trend suggests that this is so.

The Surgeon's experience is challenged by the range of evidence informing opinions, different techniques and operations to which surgeons are exposed. Surgeons engaged in contemporary sleep surgery may have different training backgrounds, for example, from an otolaryngology or maxillofacial program and there is a learning curve associated with contemporary airway surgery.

Surgical technique is critical. Reconstructive versus ablative techniques now predominate. Destructive techniques cause unwanted scar and stenosis and may lead to severe deformity and dysfunction. A recent meta-analysis looked at the role of LASER in uvulopalatopharyngoplasty and concluded that it should be used with absolute caution, or preferably not at all (82). That finding is reflective of our experience in Australia for some time, with our push for re-positioning operations and the downward trend of LASER-

type operations (83).

Anaesthetic considerations, including the notion of the shared airway, how to manage peri-operative blood pressure, extubation failure, airway oedema, post-operative analgesia and overall general anaesthetic risk in the individual patient hinge on patient factors and the experience of the operative team. A plan for management of complications and long-term follow-up must be made. Patients need to be aware of these so that unrealistic expectations are addressed.

One of the myths around the role of surgery is that harm outweighs benefits. When papers directly comparing benefits and harm are evaluated, there is high benefit noted. For example, with respect to dysphagia, 89% had no regret undergoing palate surgery despite suffering temporary dysphagia (84-86). The study on 20,000 US Veterans by Weaver *et al.* (87) showed a survival benefit of surgery over prescription (not application) of CPAP over the medium term, defined as a four-to-five-year period.

There is an accumulation of RCT evidence in surgery showing significant benefit over harm (88-90), including polysomnography (PSG) and quality of life (QOL) outcomes. However, in order to show a treatment effect with surgery, the numbers are often too small to demonstrate side effects. An Australian RCT comparing surgery with no treatment is near completion, and researchers are collecting data on high level as well as low level complications. There is further evidence for surgery based on other domains, including cardiovascular risk, mortality, motor vehicle accident risk and cost-effectiveness (91-93). However, most of this evidence is at cohort, rather than RCT level.

Another myth is that surgery is simple and easy, but the reality is that it is complex. Anatomy is complicated, function must be considered, staged procedures may be contemplated, tailored treatment is required, and recovery can be difficult. The key is in patient selection and education. A detailed consent process is undertaken involving the goals of surgery and the risks and benefits for the individual patient. The pre-operative process includes a comprehensive history and examination and evaluation of the PSG. A comprehensive discussion about alternative treatments needs to be undertaken. These include CPAP, MAS or lateral positioning devices, other surgeries (including bariatric) and horizonal treatments.

A further myth is that surgeons just operate. While some do, most do not. Informed consent is fundamental. Most surgeons will discuss alternatives to surgery and remain thoughtful in their approach to the patient. Often, the role of the surgeon is to counsel against surgery.

Sleep surgery tools such as the medical checklist by Camacho *et al.* (94) provide a detailed template for evaluation of the patient and are useful in identifying patients who are not suitable for surgery.

Other controversies and challenges in surgery include the ethics of lack of treatment over time and the impact of patient versus clinician directed treatment. The assessment of cardiovascular risk to the patient, particularly in the context of the recent SAVE trial is vexed (19). The threshold for surgical intervention is challenging, as discussed by Rotenberg *et al.* in his Triological Thesis (95). He looked at improved QOL parameters, PSG parameters and blood pressure outcomes with surgery and suggested that some patients could be offered surgery earlier in their disease, rather than pursuing device use.

Current concepts of the role of surgery in OSA is in failed compliance or intolerance to device use, and in significant complications arising from device use. Open to further discussion, research and debate is the role of surgery when the patient favours it, and those with favourable anatomy for surgery. Newer modalities for patient selection including predictive medicine tools may help us select these patients earlier. In summary, a balanced assessment is critical, and comprehensive training and experience is paramount.

In summary, all treatments in adult OSA carry risk, and trained clinicians are critical in outlining potential benefits versus complications. Patient education and engagement is integral to the treatment process.

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