

Nasal Expiratory Positive Airway Pressure (EPAP) for the Treatment of Obstructive Sleep Apnea: A Review of Clinical Studies of Provent Therapy

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Abstract

Nasal EPAP (Provent Therapy) represents an important, new treatment option for many patients with obstructive sleep apnea (OSA). A series of peer-reviewed published articles have demonstrated clinically and statistically significant reductions in apnea hypopnea index (AHI), oxygen desaturation index (ODI) and sleepiness as well as high patient acceptance and compliance. This review is intended to provide healthcare providers an overview of the available clinical data to support use of this new class of therapy. The mechanism of action of nasal EPAP and patient selection recommendations are also discussed. Finally, the role of the healthcare provider in helping the patient to acclimate to nasal EPAP is highlighted, along with recommendations to optimize patient acceptance of the therapy.

Introduction

Obstructive sleep apnea (OSA) is a common medical condition that can be associated with a variety of symptoms and morbidities. OSA frequently results in excessive daytime sleepiness, which is associated with an increased risk of motor vehicle accidents.^{1,2} OSA has also been linked to hypertension, stroke, congestive heart failure, cardiac arrhythmia and depression.³⁻⁶

The gold standard treatment of OSA, continuous positive airway pressure (CPAP), is effective for any severity of OSA as long as the patient remains compliant with therapy. However, CPAP therapy can be cumbersome, noisy and uncomfortable and many patients either cannot tolerate CPAP at all, or only use it sporadically. It has been reported that 46 to 83% of patients with OSA are non-adherent to CPAP treatment.⁷ Thus, while CPAP is highly efficacious in a laboratory setting, it is not used regularly at home by a large proportion of patients. Additionally, one recent study showed that 94% of patients who had rejected CPAP were interested in new treatment options.⁸ These data underscore the need for alternative therapies.

Response to non-CPAP therapies is typically either expressed as the percentage of patients who achieve $\geq 50\%$ AHI reduction or who achieve an AHI of less than 10. The basic treatment principle of OSA is to maximally reduce the AHI, recognizing that achieving an AHI of less than 10 may not be possible in all patients, especially those with severe OSA. In these cases,

a partial AHI reduction may be better than non-treatment. Furthermore it is recognized that OSA is a chronic disease that must be treated by the patient over that patient's lifetime. Thus a goal of successful treatment is to prevent as many breathing disturbances as possible which requires both efficacy and utilization. A treatment that prevents 100% of the abnormal events in the laboratory but is used by the patient only half of sleep time may be considered only 50% effective.

Recently, nasal EPAP has become broadly available for patients with OSA. The earliest use of EPAP to treat OSA dates back to 1983 when Mahadevia et al demonstrated that the passive application of 10cm H₂O of EPAP could significantly improve the apnea index and oxygen desaturation index.⁹ More recently, a series of well designed prospective studies have demonstrated the efficacy of nasal EPAP for the treatment of OSA.

The only FDA cleared nasal EPAP product indicated to treat OSA is known as Provent Therapy (Ventus Medical, Belmont, CA) [Figure 1]. The device has been evaluated in multiple published studies and has been shown to be clinically effective in treating mild, moderate and severe OSA. The device consists of a small valve attached externally to each nostril with hypoallergenic adhesive. The valve acts as a one-way resistor, permitting unobstructed inspiration. During expiration, the airflow is directed through small air channels, increasing the resistance. This increased resistance during expiration creates EPAP which is maintained until the start of the next inspiration. Whereas CPAP provides positive pressure during both inspiration and expiration, EPAP only creates pressure during expiration.

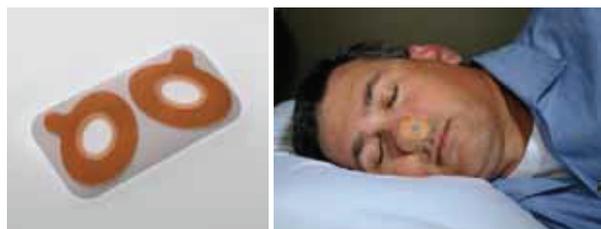


Figure 1. Provent Sleep Apnea Therapy (Courtesy Ventus Medical)

Nasal EPAP Mechanism of Action

OSA is traditionally thought of as an inspiratory disease. However, it is important to note that the closure of the upper airway has its origins at the end of expiration, when the pressure in the airway is zero. Morrell et al showed that upper airway cross sectional area progressively decreased in the four breaths

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prior to an obstructive apnea, with this area being smallest at end-expiration. Their conclusion was that this expiratory narrowing made it more likely for the airway to completely collapse during the subsequent inspiration.¹⁰ Provent nasal EPAP creates increased expiratory pressures which are maintained through the end of expiration and until the start of the subsequent inspiration [Figure 2].

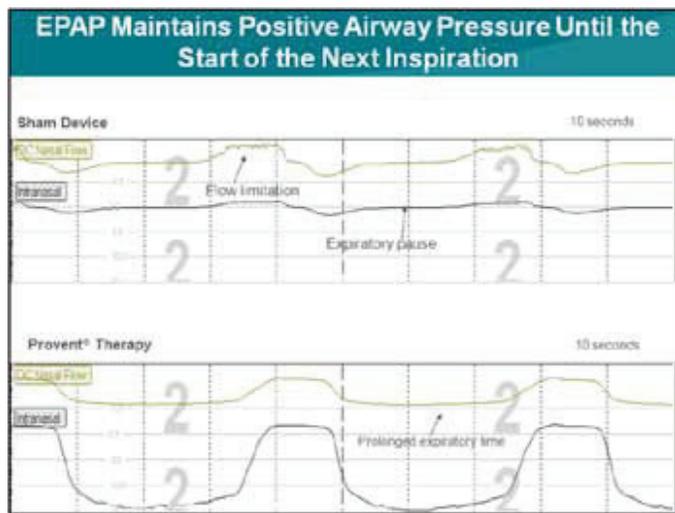


Figure 2: These PSG waveforms demonstrate Provent nasal EPAP's effects on breathing. The top panel shows an untreated subject (wearing a sham device). The bottom panel shows the same subject wearing Provent nasal EPAP. Both nasal air flow (inspiration up, expiration down) and intranasal pressures (in cm H₂O) are shown. When Provent device is not worn, there is clear inspiratory flow limitation. Intranasal pressures remain about zero during most of the expiratory time--showing a clear end-expiratory pause. In contrast, with Provent nasal EPAP, expiration is prolonged and there is positive intranasal pressure of at least 10 cm H₂O maintained until the start of the next inspiration. The end-expiratory pause has been eliminated. (Courtesy Ventus Medical).

The exact mechanism through which nasal EPAP treats OSA is still unclear, but several mechanisms appear most likely:

- 1) Positive end-expiratory pressure (PEEP) leading to increased end-expiratory lung volumes (or FRC) that increases longitudinal traction on the pharynx, rendering it less collapsible ("tracheal tug").¹¹ Indeed, the role of increased lung volumes in decreasing the compliance of the upper airway has been well described in the literature.¹²
- 2) Dilatation of the upper airway by EPAP which carries over until the start of the next inspiration.¹³
- 3) Mild hypercapnia due to hypoventilation which would lead to increased respiratory drive to the upper airway.¹³

It is possible that a combination of more than one of these mechanisms may be responsible for the therapeutic benefit of nasal EPAP.

The first clinical study intended to help elucidate the mechanism of Provent nasal EPAP was conducted by Colrain et al.¹⁴ This study demonstrated that the benefits of the Provent device were due to EPAP, since a similar sham device did not lead to reductions in either AHI or ODI. In a larger study by Patel et al, the authors concluded that those patients who were able to generate and sustain positive end expiratory pressures were more likely to exhibit a therapeutic response.¹³ They concluded that the primary mechanism of action was likely related to increased FRC (functional residual capacity) leading to a

tracheal traction mechanism, though they cited the possibility of a carryover effect of pressures from end-expiration into the subsequent inspiration as well as increased CO₂.

A follow up study by the same group¹⁵ concluded nasal EPAP resulted in significant hyperinflation (higher end-expiratory lung volume) during wakefulness, that there was a trend toward expiratory upper airway dilatation which appeared to carry over into inspiration and that there was significant hypoventilation and hypercapnia induced both while awake and asleep. Additional mechanistic studies are ongoing and will provide additional insights into the mechanism of action of Provent nasal EPAP.

Review of Provent Therapy Clinical Studies

Provent Therapy has been studied in a series of prospective clinical studies. Several are highlighted below:

A novel nasal expiratory positive airway pressure device for the treatment of obstructive sleep apnea: a randomized controlled trial¹⁶ –Berry RB, Kryger MH, Massie CA. [SLEEP 2011; 34:479-485]

250 OSA patients from 19 centers were enrolled in this prospective, multicenter, parallel-group, sham controlled, randomized double-blind trial with three month follow up. Patients were enrolled and randomized to a sham or Provent group. During the first week of treatment, patients underwent 2 in-lab PSGs on non-consecutive nights (one device-on, one device-off in randomly assigned order). After three months of treatment, patients underwent another two in-lab PSGs with the device on and device off. Outcomes included a comparison of the difference in the AHI between device-on and device-off nights in the Provent and sham groups at week one and at three months.

Using an intent-to-treat analysis, at three months the percentage decrease in the median AHI was 42.7% in the Provent group compared to 10.1% in the sham group (p<0.0001). Treatment effect by severity is shown in Figure 3. Provent nasal EPAP reduced the median AHI from 8.8 to 3.9 in mild OSA patients (p<0.001), from 20.5 to 8.4 in moderate OSA patients (p<0.001) and from 48.2 to 18.9 in severe OSA patients (p<0.001). At month three, treatment success (defined as at least a 50% reduction in the AHI or an AHI of less than 10) was achieved in 50.7% of patients in the Provent nasal EPAP group. Based on patient self-report, the median percentage of nights the EPAP device was used for the entire night was 88.2%. There were no serious device related adverse events reported. The authors concluded that Provent nasal EPAP is an effective treatment alternative for a substantial percentage of the OSA population.

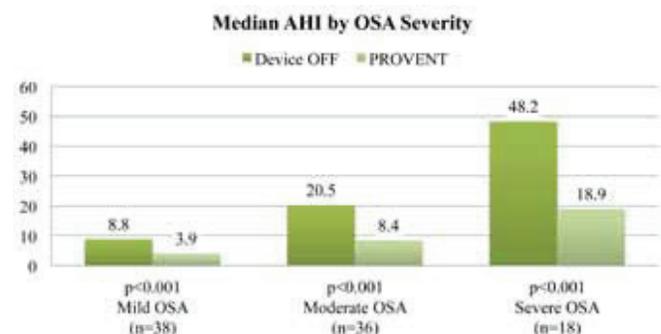


Figure 3. AHI reduction by OSA severity¹⁷

A convenient expiratory positive airway pressure nasal device for the treatment of sleep apnea in patients non-adherent with continuous positive airway pressure¹⁸ –Walsh JK, Griffin KS, Forst EH, et al. [Sleep Medicine 2011;12:147-52]

This study focused on OSA patients who were non-adherent to CPAP. Most patients had moderate to severe OSA, with over half of the patients having a baseline AHI ≥ 30 . A total of 59 patients with OSA who refused CPAP or used CPAP for less than 3 hours per night were provided the Provent nasal EPAP device, of which 47 patients (80%) tolerated the device. Patients then underwent baseline sleep studies and 43 of these patients met enrollment criteria. Of these 43 patients, 24 (56%) met efficacy criteria based on AHI and symptom response. The responding patients continued on the device for 5 weeks, followed by a final in-lab PSG to verify ongoing efficacy. The mean baseline AHI in these patients was 31.9 which decreased to 16.4 at 5 weeks. The Epworth Sleepiness Scale improved from a baseline of 12.3 to 8.7 ($p=0.001$). Device use was reported an average of 92% of all sleep hours. This study in non-adherent CPAP patients demonstrated that nasal EPAP can lead to improvements in AHI and sleepiness, along with a high degree of treatment adherence.

A multicenter, prospective study of a novel nasal EPAP device in the treatment of obstructive sleep apnea. Efficacy and 30-day adherence¹⁹ –Rosenthal L, Massie CA, Dolan DC, et al. [Journal of Clinical Sleep Medicine 2009;5:532-37]

This multicenter prospective study was specifically designed to assess adherence over a 30 day period, and also evaluated efficacy based on serial in-lab PSG studies. A total of 34 patients with OSA underwent a 30 day trial of the Provent nasal EPAP device. Patients kept a daily log and weekly phone calls were conducted by study staff. Participants reported using the Provent nasal EPAP device all night long for 94.4% of the possible nights during the in-home trial. The 30 day study demonstrated a significant improvement in AHI ($p=0.001$) and symptomatic improvement as measured by Epworth Sleepiness Scale ($p<0.001$) and Pittsburgh Sleep Quality Index ($p=0.042$). Percentage of the night spent snoring was also reduced significantly ($p=0.013$). The authors concluded that treatment with nasal EPAP was well tolerated and accepted by patients in the study.

A pilot evaluation of a nasal expiratory resistance device for the treatment of obstructive sleep apnea²⁰ –Colrain IM, Brooks S, Black J. [Journal of Clinical Sleep Medicine 2008;4(5):426-433]

Colrain et al were the first to publish clinical results of the Provent nasal EPAP device. Thirty patients (24 with OSA, 6 with primary snoring) underwent 2 nights of in-lab PSG, with and without the EPAP device with the order of nights counterbalanced to minimize first night effect. The studies were scored blind to treatment condition. The AHI ($p<0.001$) and ODI ($p<0.01$) both significantly decreased, and the percentage of the night spent above 90% saturation ($p<0.05$) increased significantly with device use. The observed duration of snoring significantly decreased ($p<0.001$) with nasal EPAP use.

Predictors of response to a nasal expiratory resistor device and its potential mechanisms of action for treatment of obstructive sleep apnea¹³ –Patel AV, Hwang D, Masdeu MJ et al [Journal of Clinical Sleep Medicine 2011;7(1):13-22]

This study sought to provide data to better understand the potential mechanisms of action of Provent nasal EPAP. Twenty patients with OSA underwent 3 in-lab PSGs including diagnostic, therapeutic (Provent), and CPAP studies. Intranasal pressures, PCO_2 , closing pressures (Pcrit), and awake lung volumes in different body positions were also measured. There were significant reductions in AHI ($p<0.05$) and RDI ($p<0.0001$) with Provent nasal EPAP compared to the diagnostic study. No significant predictors of therapeutic response were found. Successful treatment of breathing events was associated with creation and maintenance of elevated end expiratory pressure. The authors concluded that Provent nasal EPAP can treat sleep disordered breathing across the full spectrum of severity.

Long term use of a nasal expiratory positive airway pressure (EPAP) device as a treatment for obstructive sleep apnea²¹ –Kryger MH, Berry RB, Massie CA [SLEEP Abstract Supplement, 2011 (34):A118]

This 13 center study was an extension of the three month (Berry et al) study and designed to evaluate the long-term effectiveness of Provent nasal EPAP after 12 months of follow-up. 41 patients from the Provent arm of the three month study who met adherence and efficacy criteria were continued on therapy and returned for in-lab PSG after 12 months of treatment. Results from these 12 month PSGs were compared against their baseline results. Median AHI was reduced from 15.7 to 4.7 (baseline device-off versus month 12 device-on). The AHI (median) reduction was 71.3% ($p<0.001$). Percentage of time snoring was reduced by 74% ($p<0.001$). The Epworth Sleepiness Scale decreased from 11.1 ± 4.2 to 6.0 ± 3.2 ($p<0.001$) over the twelve months of study. The median percentage of nights patients reported using the device the entire night was 89.3%. The authors concluded that Provent nasal EPAP significantly reduced the AHI and snoring and improved daytime sleepiness after 12 months of treatment. Long-term compliance was deemed excellent.

Additionally, several retrospective studies demonstrating the acceptance and efficacy of Provent nasal EPAP were recently presented at the 2011 Annual Meeting of the Associated Professional Sleep Societies:

Retrospective cases series analysis of a nasal expiratory positive airway pressure (EPAP) device to treat obstructive sleep apnea in a clinical practice²² –Adams, G. [SLEEP Abstract Supplement, 2011 (34):A146]

This retrospective analysis was completed to evaluate patient acceptance and AHI reduction using Provent nasal EPAP in a real world clinical practice. OSA patients (with AHI >10) received 10 nights of EPAP devices for in-home evaluation. Patients that acclimated returned for efficacy confirmation using standard in-lab PSG. During these treatment PSGs, adjunctive therapy such as positional therapy or chin straps was used, when necessary, to optimize treatment effect. 151 patients sampled nasal EPAP and 131 were in the analysis group. Of the analysis group, 75% acclimated to the device. The median AHI was reduced from 25.8 to 4.2 ($p<0.001$). A treatment AHI <10 was achieved in 80.7% of all patients and 90.6% of those with mild/moderate OSA. The author concluded that Provent nasal EPAP achieved statistically significant improvements in AHI and that treatment acceptance was excellent.

Nasal EPAP as a major therapeutic option in a clinical sleep center setting²³ –Hwang D, Becker K, Chang J, et al. [SLEEP Abstract Supplement, 2011 (34):A146]

This analysis reported a single clinical sleep center's (Kaiser Permanente, Fontana, CA) experience using Provent nasal EPAP as a treatment option for OSA patients who were intolerant of CPAP. Patients underwent a clinic orientation session, in-home acclimation trial, and portable monitoring to confirm effectiveness. A total of 94 OSA patients were offered nasal EPAP; 86 patients (91.5%) continued with in-home evaluation. 36 (41.9%) returned for a nasal EPAP post-test study using portable monitoring. Among those completing a post-test, AHI was reduced from 22.7 to 8.9 ($p < 0.00001$) and ODI 4% from 21.8 to 12.1 ($p = 0.002$). Treatment response rate for mild, moderate and severe OSA patients was 63.6%, 70.0%, and 38.5% respectively. The authors concluded that Provent nasal EPAP is an important therapeutic option for the treatment of OSA.

Clinical efficacy of a nasal expiratory positive airway pressure (EPAP) device for the treatment of obstructive sleep apnea²⁴ – Massie C, Hart RW. [SLEEP Abstract Supplement, 2011 (34):A146]

This retrospective analysis included OSA patients in a community based sample that were treatment naive, or had previously tried and rejected CPAP. Of patients offered Provent nasal EPAP, 64% had rejected CPAP, 32% were treatment naive and 4% had tried non-CPAP therapies. In the 70 patients in which follow up was completed, 41 (59%) accepted therapy after an initial trial period. An additional 11 were continuing with Provent nasal EPAP therapy based on subjective symptom response and repeat physician evaluation. PSG data for 30 patients with paired PSG data sets revealed a treatment success of 80% (24 patients). Treatment success was defined as a decrease in AHI $\geq 50\%$ or an AHI < 10 . Median AHI was reduced from 17.1 to 4.9 ($p < 0.001$) and there was a trend toward lower Epworth scores [7.2 to 5.5 ($p = 0.07$)]. The authors concluded that the Provent nasal EPAP device is both an effective and well tolerated treatment option for mild to moderate OSA patients or for patients who have rejected CPAP.

Responder Analysis

A pooled analysis of the data from the first five published Provent nasal EPAP studies¹⁷ shows that 57% of patients in the analysis are responders (defined by AHI improvement $> 50\%$) and another 11% of patients are partial responders (defined by AHI improvement of 30-50%) [Figure 4].

Pooled Analysis of Provent Therapy Responders (published studies)

Response to Provent Therapy

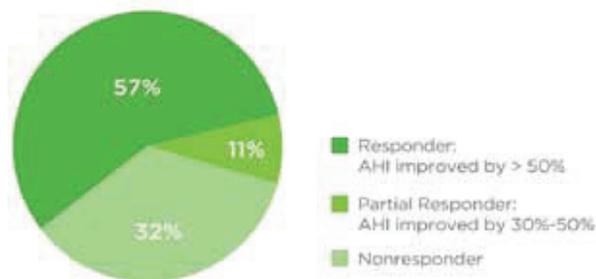


Figure 4. Pooled analysis of Provent Therapy Responders, based on data from the first five published studies¹⁷

It is important to note that patients in clinical practice should confirm efficacy of the Provent nasal EPAP device since response can vary from patient to patient, as the pooled analysis confirms. In-lab PSG or portable monitoring are preferred. A specialized Provent cannula that snaps onto the nasal EPAP device may be used and can interface with standard PSG and portable monitoring equipment [Figure 5]. The use of confirmatory testing is helpful in quickly assessing which patients are receiving adequate treatment response. Responders to Provent nasal EPAP have an average of 72% reduction in AHI, with a mean treatment AHI of 7.3 [Figure 6].

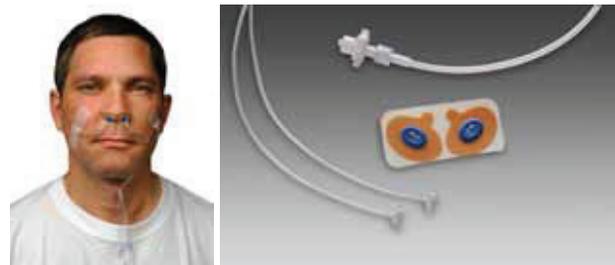
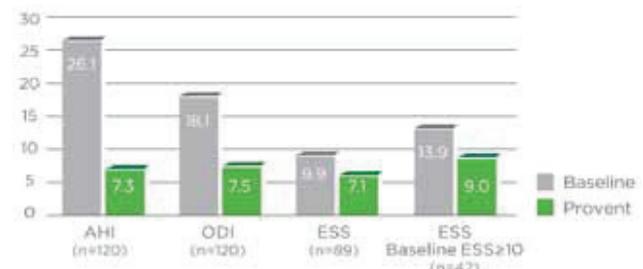


Figure 5. The Provent nasal cannula can be used with in-lab PSG or portable monitors

Mean Apnea Hypopnea Index (AHI), Oxygen Desaturation Index (ODI) and Epworth Sleepiness Scale (ESS) in Responder Subgroup



Mean AHI by Severity in Responder Subgroup

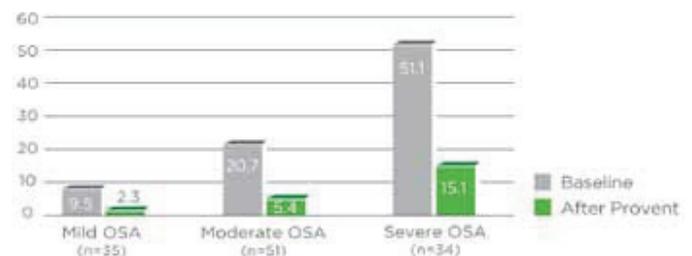


Figure 6. Mean AHI, ODI, and ESS in a responder subgroup, based on pooled data from the first five published Provent nasal EPAP studies¹⁷

Real World Implications

Recommended patients for Provent nasal EPAP include:

- 1) Patients (mild, moderate or severe) who have rejected or are non-compliant with prescribed CPAP
- 2) Newly diagnosed mild/moderate OSA patients without significant co-morbidities
- 3) CPAP compliant patients looking for alternatives for travel

As noted previously, CPAP is considered the gold standard treatment for OSA and is associated with an excellent response rate based on reductions in AHI. However, many patients are

not tolerant of or compliant with CPAP and alternative therapies must be considered. OSA treatment alternatives include Provent nasal EPAP, oral appliances and various surgical interventions. Each of the alternative OSA therapies requires confirmatory testing to determine efficacy. However, a trial of Provent therapy requires minimal investment compared to a custom oral appliance (averaging >\$1000 per appliance) or surgical intervention. Finally, real world compliance of Provent nasal EPAP can be tracked by monitoring the frequency of refills.

The Importance of Acclimation

It may take several days for patients to acclimate to wearing and breathing through the Provent nasal EPAP device. The healthcare provider plays an important role in setting acclimation expectations for the patient as well as providing important recommendations to facilitate acclimation. These include:

- 1) Informing the patient that the first few nights using nasal EPAP may be difficult, but that it improves over the ensuing days
- 2) Suggesting the patient remove the device during initial nights if he/she has difficulty sleeping with the device
- 3) Instructing the patient to breathe through the mouth while awake and falling asleep
- 4) Letting the patient know it may take up to ten nights or more to acclimate to the device

Summary

Multiple clinical studies of Provent nasal EPAP have been published including a large sham-controlled randomized trial. These studies have consistently demonstrated that the device is associated with excellent compliance and highly significant reductions in AHI in patients with mild, moderate and severe OSA, including patients who have previously failed CPAP. Snoring reductions and improvements in sleepiness have also been consistently demonstrated across these studies. Provent nasal EPAP represents an important new treatment option for patients with OSA and the healthcare providers who care for them.

Disclosures

Dr Doshi is the Chief Scientific Officer of Ventus Medical. Dr Westbrook is the Chief Medical Officer of Ventus Medical and Advanced Brain Monitoring, a manufacturer of portable sleep recording equipment.

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