NEW RESEARCH

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SCIENTIFIC INVESTIGATIONS

Pharmacological Treatment of Obstructive Sleep Apnea with a Combination of Pseudoephedrine and Domperidone

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Study Objectives: To determine the effect of the drug combination domperidone and pseudoephedrine on nocturnal oximetry measurements and daytime sleepiness in patients with obstructive sleep apnea.

Methods: We recruited patients with severe snoring and apneic episodes willing to undergo repeated nocturnal oximetry testing. Following baseline clinical history, Epworth Sleepiness Scale administration, and home overnight nocturnal oximetry, patients were started on weight-adjusted doses of domperidone and pseudoephedrine. Follow-up oximetry studies were performed at the patient's convenience. On the final visit, a repeat clinical history, Epworth score, and oximetry were obtained.

Results: Seventeen of 23 patients noted disappearance of snoring and apneic episodes. Another 2 patients reported improvement in snoring and no apneic episodes. All but one patient had a decrease in Epworth scores (mean decrease 9.4 (95% CI, 6.8-12.1, p < 0.0001). Mean oxygen saturation (2.5; 95% CI, 0.66-4.41, p = 0.008), percent time with oxygen saturation < 90% (14.8; 95% CI, 24.4 to 5.2, p = 0.003), and the 4% oxygen desaturation index (18.2; 95% CI, 27.3 to 9.1, p < 0.0001) improved significantly. No adverse effects of treatment were noted.

Conclusions: The combination of domperidone and pseudoephedrine improved self reported snoring and sleepiness, and may have improved apneic episodes and sleep-related nocturnal oxygen desaturation in patients with obstructive sleep apnea provided the proportion of time spent asleep did not diminish. This drug combination warrants further study as a treatment for obstructive sleep apnea.

Keywords: Obstructive sleep apnea; oximetry; sleepiness; domperidone; pseudoephedrine; pharmacotherapy; desaturation; treatment

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Obstructive sleep apnea (OSA) is a common disorder that is characterized by sleep disordered breathing due to upper airway obstruction. Individuals with OSA may present with complaints of sleepiness, unrefreshing sleep, fatigue, or insomnia.[1] OSA is associated with or may cause a number of chronic health problems including hypertension, cardiovascular and cerebrovascular problems, neurocognitive deficits, and metabolic dysfunction.[2-4] Although the diagnosis of OSA typically requires polysomnography, the presence of habitual and loud snoring associated with witnessed apneas is a primary clinical manifestation of the disorder.[1]

A commentary on this article appears in this issue on page 124.

In a recent randomized controlled study of subjects complaining of severe snoring, we demonstrated that the combination of domperidone and pseudoephedrine was effective in improving or eliminating snoring.[5] Half of the subjects in this study were noted by their sleeping partners to have episodes of apnea. Many of the study subjects also complained of fatigue and somnolence, suggesting that they suffered from OSA. After successful treatment of their snoring, the majority of the subjects reported both a return of vigor and well-being and a disappearance of witnessed apneas.

Domperidone is a drug with peripheral anti-dopaminergic (D1 and D2) activity.[6] The drug has prokinetic effects and may have some efficacy in the treatment of gastroesophageal reflux. We hypothesized that gastroesophageal reflux might contribute to snoring and, thus, chose this agent, in part, to reduce any reflux that might contribute to snoring.

The treatment of reflux is not the only mechanism by which domperidone may reduce snoring and sleep apnea. Dopamine acts as an inhibitory neurotransmitter in the mammalian carotid body. Animal studies have demonstrated that domperidone enhances hypercapnic ventilatory response and carotid chemosensory discharge response to hypercapnia.[7,8] A study in patients with OSA showed hypercapnic ventilatory response and peripheral chemosensitivity were increased by administration of domperidone in the patients with OSA.[9]

BRIEF SUMMARY

Current Knowledge/Study Rationale: The combination of domperidone and pseudoephedrine was previously demonstrated to be effective in improving or eliminating snoring in patients complaining of severe snoring. We sought to determine the effect of the drug combination on sleep disordered breathing and daytime sleepiness in patients with OSA.

Study Impact: The combination of domperidone and pseudoephedrine shows promise as a treatment for OSA. In view of the clinical importance of OSA and the need for a simple effective therapy of this disorder, it is hoped that these observations will stimulate interest and further study of this drug combination.

Table 1—Clinical characteristics.

#	Age/ Sex	Clinical characteristics	BMI	Reflux	Nasal
1.	46 M	Snoring/apneas × 10 y; PSG: 68 apneas/h	32.9	Mod	Sev
2.	58 F	Snoring × 20 y; apneas × 19 y	29.7	Mod	No
3.	72 M	Years of snoring; apneas × 3y	23.7	Sev	Mod
4.	52 F	2 PSG with OSA; CPAP × 7 mo; failed uvuloplasty	30.4	No	Sev
5.	54 M	2 PSG with OSA; hypertension	28.8	Mild	Sev
6.	45 F	Hypertension	28.1	Mild	Mod
7.	44 M	Snoring/apneas × y; fell asleep driving × 2	31.1	Mild	Mild
8.	59 M	Snoring × y; apneas × 15 y	25.5	No	Mild
9.	52 M	Apneas × 5 y; on CPAP	34.6	No	Mild
10.	36 M	Apneas × y	33.3	Mild	Mild
11.	43 M	Snoring/apneas	32.4	No	Mild
12.	47 M	Snoring/apneas × y; uvulectomy; sinusitis	26.8	No	Mod
13.	37 M	Snoring × y; apneas × 5 y	29.4	Mild	Mild
14.	30 M	Snoring/apneas × 5 y; PSG with > 10 apneas/h	31.1	Mild	Sev
15.	66 M	Snoring × y; apneas	25.7	Mild	Mod
16.	37 M	Apneas; CPAP	27.3	No	No
17.	54 M	Severe snoring × y; many apneas	25.2	Mild	Mild
18.	55 M	Severe snoring and apnea × y	24.6	Mild	Mod
19.	47 M	PSG with OSA	28.0	Mild	Sev
20.	53 M	Snoring/ apneas × y	26.8	Mild	Mild
21.	25 M	Snoring/ apneas × 7 y	27.8	Mild	Sev
22.	35 M	Snoring × y; apneas × 5 y	31.0	Mild	Mild
23.	59 M	Snoring × y; apneas × 5 y	27.2	No	Sev

Reflux, Symptoms of gastroesophageal reflux; Nasal, Presence of nasal congestion; Mod, Moderate; Sev, Severe; PSG, Polysomnogram; y, Years

Pseudoephedrine, an α-adrenergic agonist commonly used to treat nasal congestion, was chosen because nasal congestion can contribute to snoring and sleep disordered breathing. Our placebo-controlled trial of this drug combination showed that the combination improved snoring more than either component alone.[5] This suggests that each component may play an active role in the amelioration of sleep disordered breathing.

Since OSA is a sleep state dependent disorder, it should theoretically be amenable to pharmacological therapy targeting the sleep dependent neurochemical changes.[10] A recent review of pharmacological therapy in OSA concludes that there is no consistently effective therapy.[11] Based on our preliminary evidence that the drug combination might treat OSA, we decided to assess whether objective measures of sleep disordered breathing and the Epworth Sleepiness Scale score improve with therapy.[12] We present a case series of patients with severe snoring, witnessed apneas, and daytime fatigue who underwent continuous nocturnal oximetry and completed the Epworth Sleepiness Scale before and after drug therapy.

METHODS

Subjects

During the period from September 2006 to April 2008, a total of 180 patients being evaluated for severe snoring, witnessed apneas, and fatigue at the Clinica Servet in Santiago, Chile underwent at least one nocturnal oximetry study. Twenty-three patients with Body Mass Index (BMI) < 35 who were willing to have repeat oximetry performed while on combination therapy were included in this case series. Their clinical characteristics are shown in **Table 1**. All patients had periods of witnessed apnea. Five subjects reported having a previous diagnosis sleep apnea by polysomnography, and 3 subjects reported having used CPAP. All subjects understood that their study results would be coded and used for research purposes. The study was approved by the chairman of the Institutional Review Board of the Clinica Servet.

Measurements

Clinical Observations

A brief clinical history concerning duration and intensity of snoring and the presence or absence of witnessed apnea was obtained by the clinician. The presence or absence of severe snoring and apnea events was ascertained by the patient's bed partner's report. The Epworth Sleepiness Scale (English version) was administered at baseline and final visits.[12] Weight was measured at baseline and at least one follow-up visit.

Oximetry

Subjects had overnight pulse oximetry in their homes. The pre-drug study was obtained for clinical reasons; post-drug studies were scheduled at the convenience of the subjects. The patients applied the oximetry sensor to the index finger, and connected the lead to an oximeter (Masimo Rad-8 with 2-sec resolution). The records obtained were analyzed by the software (Profox Oximetry Version Masimo 0706.05N; Profox Associates, Inc. Pennsylvania). The tracings were scanned manually for breaks in the record caused by sensor displacement; if found, they were removed before analysis of the tracings. The investigators editing the tracing were not blinded to treatment status. There was no increase in artifact noted on tracings after drug treatment. Clinical data, Epworth scores, and oximetry tracings were coded before being sent to Seattle for analysis.

The program provided values for the mean oxygen saturation, the lowest oxygen saturation, the percent time that saturations were below 90% (CT90%), and the 4% oxygen desaturation index (ODI).

Treatment

Typically within 10 days after the pre-treatment record was obtained, the patients received either one or two capsules containing 10 mg of domperidone and 60 mg of pseudoephedrine sulfate. The number of capsules was determined by the patient's BMI. Those with a BMI < 28 received one capsule. Patients with a BMI between 28 and 30 received one capsule for 3 to 5 nights; an extra capsule was added if there was no improvement in snoring; patients with BMI > 30 received 2 capsules. They were instructed to take the pills at bedtime.

Statistical Analysis

The average change in Epworth score from baseline was calculated by taking the difference in baseline score and the score at last follow-up and averaging these differences across all 23 subjects. The null hypothesis that this difference was zero was tested using the one-sample *t*-test. Linear regression was also used, so that the average change could be adjusted for length of follow-up. The dependence of change in Epworth score on dose was assessed with a 2-sample *t*-test. Change from baseline in various oximetry parameters (mean SpO_2, CT90%, and ODI) was assessed using generalized estimating equations (GEE).[13] Each subject had multiple measurements following the start of treatment, and GEE allowed measurements within a subject to be analyzed as a cluster rather than treating each observation as coming from independent subjects. For each post-treatment measurement, the change from baseline was calculated and the average change from baseline was estimated using GEE. To assess the dependence of this change on dose, a factor indicating one or two capsules was included in the GEE regression model. No adjustments were made for multiple comparisons.

RESULTS

All patients tolerated the medication combination well. Sixteen patients had complete resolution of snoring and periods of apnea. Three patients (#5, #6, and #16) continued mild snoring but had no more periods of apnea. Four patients (# 7, #17, #18, and #19) continued to exhibit snoring and periods of apnea. Abnormal Epworth scores improved in almost all patients (**Table 2**). The mean Epworth score at baseline was 14.1, and the mean score at last follow-up was 4.2. The average decrease in Epworth scores from baseline to last score was 9.9 (7.2-12.6, $p < 0.0001$). The changes are graphed in **Figure 1**.

The mean decrease in Epworth score among subjects who received 1 capsule was 8.1 ($n = 11$, $p = 0.0008$). The mean decrease in Epworth in subjects who received 2 capsules was 11.5 ($n = 12$, $p = 0.0002$). While the difference (8.1 vs. 11.5) was suggestive of a dose effect, it was not statistically significant ($p = 0.24$). The statistical power to observe a significant difference, however, is obviously limited with such a small sample size ($n = 11$, $n = 12$). Nine patients had weight loss during the study period, ranging from 2 to 15 kilograms.

Table 3 presents the oximetry values obtained during the study. In addition to the recorded values, an opportunity to restudy patient 1 at 21 months of therapy showed that the mean oxygen value was 96.9%; the minimum oxygen value was 85%; the CT90% was 0.3; and the ODI was 0.9.

Considering the entire group, the mean SpO_2 at baseline was 92.2%, and the mean final SpO_2 was 94.2. The average improvement for all patients in mean SpO_2 was 2.5 (95% CI, 0.66-4.41, $p = 0.008$). The mean baseline CT90% was 17.7, and the mean CT90% at last measurement was 7.1. The average change from baseline CT90% was 14.8 (95% CI, 24.4 to 5.2, $p = 0.003$) (**Figure 2**). The mean ODI at baseline was 41.5, and the mean ODI at last measurement was 25.9. The mean improvement in ODI was 18.2 (95% CI, 27.3 to 9.1, $p < 0.0001$; **Figure 3**).

The mean decrease from baseline in ODI was 11.5 for subjects who received 1 capsule ($p = 0.001$). For subjects receiving 2 capsules, the mean decrease from baseline was 23.7 ($p = 0.001$). While the difference (11.5 vs. 23.7) was suggestive of a dose effect, it was not statistically different ($p = 0.13$).

The correlation coefficient of the change in Epworth score (last minus baseline measurement) and change in ODI (last minus baseline measurement) was $R = 0.56$ ($p = 0.005$).

Table 2—Details of therapy and Epworth scores.

#	Months in study	Number of capsules	Weight Change (kilos)	Pre-Rx Epworth score	Post-Rx Epworth score
1.	21	2	−15	21	1
2.	12	2	−12	24	2
3.	6	1	0	8	0
4.	11	2	−10	21	4
5.	7	2	−6	22	4
6.	8	1	−2	20	8
7.	2	2	−7	20	4
8.	10	1	0	13	2
9.	6	2	0	19	3
10.	1	2	−3	6	3
11.	2	2	−3	11	5
12.	12	1	0	7	2
13.	7	2	0	8	7
14.	6	1	0	17	1
15.	2	1	0	9	3
16.	1	2	0	5	0
17.	7	1	0	15	7
18.	1	1	0	6	9
19.	3	2	0	16	12
20.	9	1	−3.5	6	4
21.	5	1	0	14	5
22.	1	1	0	19	3
23.	5	2	0	17	5

Figure 1—Change in Epworth Sleepiness Scale score from pre-treatment to post-treatment.

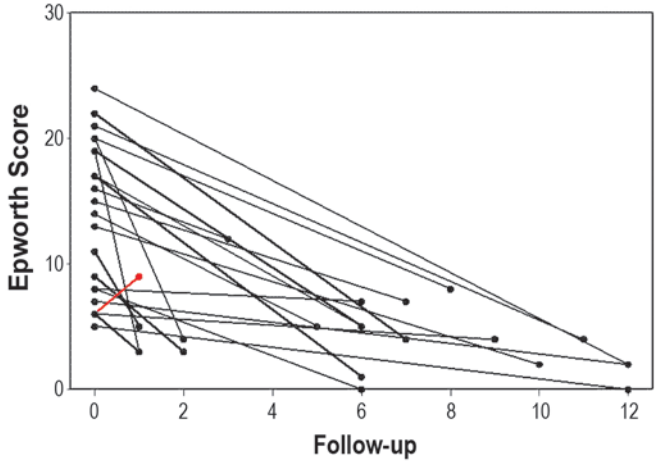


Table 3—Nocturnal oximetry values at baseline and on medication.

Pt #		Pre-drug	1 Mo	2 Mo	3 Mo	4 Mo	5 Mo	6 Mo	7 Mo	8 Mo	9 Mo	10 Mo	11 Mo	12 Mo
1	Mean	79.9		94.1		95.3		95.1				95.1		
	Low	45		68		75		80				41		
	< 90%	73.1		10.7		2.9		1.2				3.1		
	ODI	112.4		63.3		53.7		17.6				26.1		
2	Mean	90.4	92.6	94.3			94.8		95.6					95.9
	Low	61	72	74			83		79					84
	< 90%	41.0	21.7	5.6			4.9		2.9					1.4
	ODI	84.3	65.2	50.8			55.8		42.0					41.8
3	Mean	91.1	93.5	93.7		93.5		94.1						
	Low	77	69	85		86		88						
	< 90%	19.0	3.7	4.0		1.3		0.1						
	ODI	37.4	25.1	22.6		21.4		13.1						
4	Mean	93.5	94.5				94.8						93.7	
	Low	72	69				59						62	
	< 90%	9.1	3.7				5.6						9.4	
	ODI	25.4	14.6				20.9						19.7	
5	Mean	89.8	93.0	92.3			93.3		93.0					
	Low	68	71	80			74		76					
	< 90%	37.9	6.1	9.9			5.0		5.5					
	ODI	61.2	53.4	28.8			21.2		21.0					
6	Mean	93.7	94.2	94.9	94.5					95.8				
	Low	73	84	84	73					84				
	< 90%	6.2	4.5	0.9	4.1					0.1				
	ODI	55.1	41.5	14.7	52.6					51.2				
7	Mean	87.8	91.0	90.5										
	Low	55	66	52										
	< 90%	55.3	40.1	38.8										
	ODI	75.0	69.4	63.9										
8	Mean	92.3	93.9									93.8		
	Low	71	77									84		
	< 90%	5.9	1.7									1.0		
	ODI	14.9	8.0									4.7		
9	Mean	92.6	93.9					94.8						
	Low	67	71					78						
	< 90%	18.5	6.6					4.8						
	ODI	40.8	22.5					32.7						
10	Mean	93.5	94.9											
	Low	86	82											
	< 90%	1.3	0.0											
	ODI	21.4	23.0											
11	Mean	94.6	95.1											
	Low	72	79											
	< 90%	2.1	0.4											
	ODI	18.3	11.2											
12	Mean	95.5		95.2										96.8
	Low	66		81										89
	< 90%	3.7		0.9										0.1
	ODI	15.8		14.4										9.1
13	Mean	92.5	93.9	94.3					94.7					
	Low	45	56	65					69					
	< 90%	16.2	9.4	8.4					6.5					
	ODI	43.5	36.7	27.3					18.8					

Mean, Mean oxygen saturation; Low, lowest oxygen saturation; < 90%, percent time spent with oxygen saturation below 90%

Table 3 *continues on the following page*

Table 3 *(continued)*—Nocturnal oximetry values at baseline and on medication.

Pt #		Pre-drug	1 Mo	2 Mo	3 Mo	4 Mo	5 Mo	6 Mo	7 Mo	8 Mo	9 Mo	10 Mo	11 Mo	12 Mo
14	Mean	94.0	94.8					94.8						
	Low	82	82					84						
	< 90%	3.6	1.4					1.0						
	ODI	17.5	11.2					13.1						
15	Mean	92.0	91.7	91.2										
	Low	73	58	54										
	< 90%	26.6	19.1	28.3										
	ODI	48.9	32.2	46.0										
16	Mean	95.7	96.1											96.1
	Low	75	82											65
	< 90%	1.3	0.4											0.2
	ODI	6.1	5.3											4.7
17	Mean	93.7					91.5		92.4					
	Low	79					72		74					
	< 90%	6.9					26.0		18.4					
	ODI	30.1					41.4		29.9					
18	Mean	92.6	93.3											
	Low	72	80											
	< 90%	10.6	6.8											
	ODI	38.4	47.9											
19	Mean	91.1			90.4									
	Low	63			47									
	< 90%	26.5			27.1									
	ODI	66.2			52.6									
20	Mean	94.6	94.7								94.8			
	Low	73	84								83			
	< 90%	3.0	4.0								1.2			
	ODI	15.2	18.0								10.9			
21	Mean	89.3	92.0		93.8		94.0							
	Low	33	62		48		62							
	< 90%	33.7	5.0		8.4		5.0							
	ODI	56.5	19.0		31.7		19.0							
22	Mean	94.9	95.6											
	Low	82	75											
	< 90%	1.5	0.6											
	ODI	41.0	18.6											
23	Mean	94.7	94.5			94.8	94.7							
	Low	78	81			81	78							
	< 90%	3.2	2.0			2.8	3.9							
	ODI	28.0	20.3			21.3	17.0							

Mean, Mean oxygen saturation; Low, lowest oxygen saturation; < 90%, percent time spent with oxygen saturation below 90%

Patients with the most severe drops in oxygen saturation at baseline often required several months of therapy before they approached or attained normal oxygen saturation values. Once improvement occurred, it tended to be maintained during the short duration of this study. **Figure 4** shows pre and post-treatment oximetry tracings from the most severely affected patient (#1).

DISCUSSION

This unblinded, uncontrolled study of the effect of the drug combination domperidone and pseudoephedrine on subjective sleepiness and sleep disordered breathing in patients with probable OSA showed dramatic improvements in Epworth scores and clinically significant improvements in ODI, mean SpO_2, and hypoxemic burden. In addition, 16 of 23 patients had resolution of snoring and apneas by bed partner report. There was a trend to greater improvement in the Epworth score and ODI at a higher dose, supporting the explanation that the medication combination was causing the improvement. Further, there was a significant correlation between change in ODI and change in Epworth score, suggesting that reduction in sleep disordered breathing may have caused improvement in sleepiness.

Figure 2—Change in percent time with oxygen saturation < 90% from pre-treatment to post-treatment.

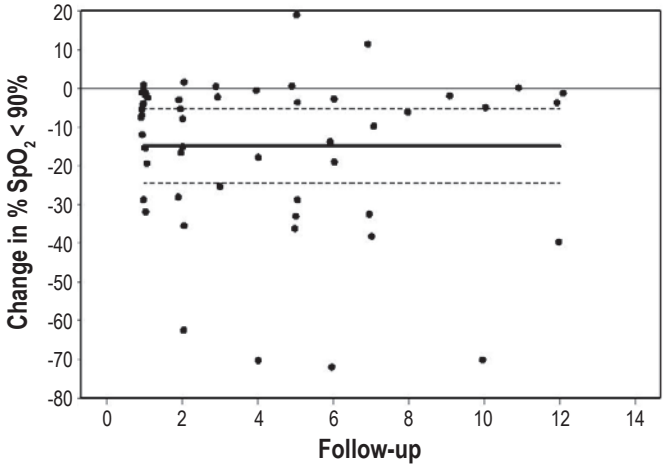


Figure 3—Change in oxygen desaturation index (ODI) from pre-treatment to post-treatment.

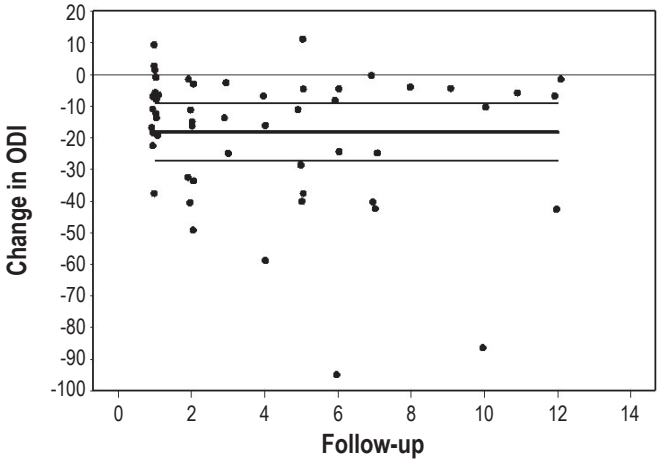
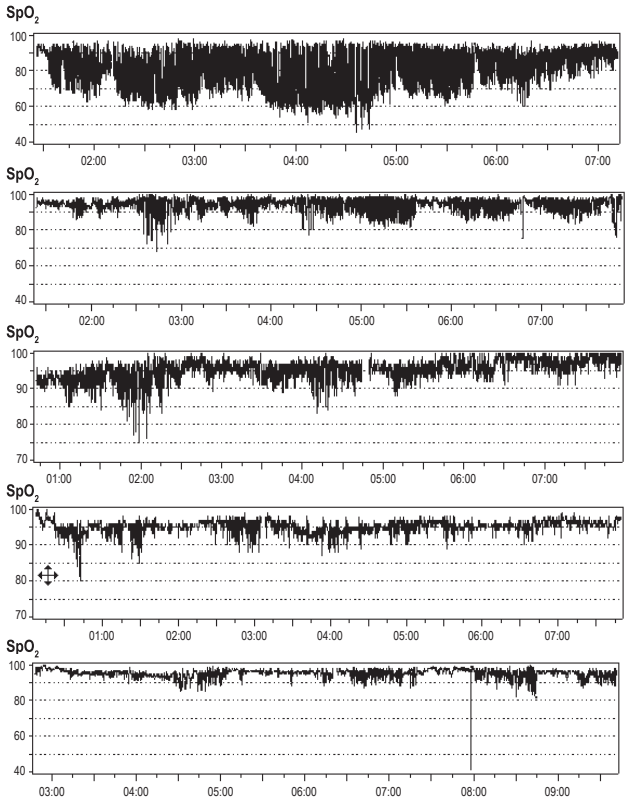


Figure 4—Sequential single night oximetry tracings on patient #1 as summarized in Table 3.



This was a retrospective case series, and therefore threats to validity such as the placebo effect and regression to the mean were not controlled for. Nevertheless, the dramatic effect seen on the oximetry values suggest that there is an effect beyond what might be expected from these explanations.

Our study has additional limitations. Polysomnography was not used to confirm the diagnosis or measure the severity of OSA. The clinical diagnosis of OSA was made in our patients because of the presence of severe snoring and episodes of witnessed apneas with associated complaints of lassitude and forgetfulness. Nocturnal oximetry studies showed frequent episodes of desaturation in a pattern consistent with the diagnosis of OSA. Studies indicate that nocturnal oximetry combined with clinical data has high specificity in identifying patients with obstructive sleep apnea.[14] The oxygen desaturation index in particular has been shown to be correlated with obstructive sleep disordered breathing severity.[15] Since sleep state was not ascertained on the night of the recording, we do not know how much of the recording time was spent asleep. It is possible that patients spent more time awake after starting the medication combination, which would have caused a reduction in ODI, though patients did not subjectively report more awake time while on the medications.

If our findings are confirmed, further study of the possible mechanisms by which OSA was ameliorated would be warranted. We do not believe that treatment of reflux and nasal congestion can fully explain the findings. Others have noted that treatment of clinically important reflux coexisting with OSA has led to improvement in symptoms and sleep disruption associated with OSA though objective measurements of sleep disordered breathing have not consistently improved.[16,17] Although the use of nasal steroids has been shown to improve sleep disordered breathing somewhat in subjects with nasal congestion, a short-acting topical decongestant did not show benefit.[11] The effect of domperidone on respiratory drive may provide an alternate mechanism by which OSA was reduced.

The safety of long-term use of pseudoephedrine and domperidone is important. There is reason for concern about the use of pseudoephedrine with regards to its cardiovascular effects. Long-term studies of pseudoephedrine use are sparse though the use of pseudoephedrine has been reported to cause atrial fibrillation, hypertension, minor tachycardia, hypotension, myocardial infarction, and premature ventricular contractions.[18] Its use is contraindicated in patients with severe coronary artery disease or hypertension and should be used with caution in patients with arrhythmias and ischemic heart disease. Common non-cardiac side effects include insomnia, anxiety, and restlessness.[18]

Domperidone does not significantly cross the blood-brain barrier in healthy individuals; however, it has been shown to counter effects of dopaminergic agents in individuals with Parkinson disease.[19] The most common adverse effects reported in controlled trials include prolactin-related effects, headache, diarrhea, somnolence, and abdominal pain; and most adverse effects are reported to resolve with continued therapy or are well tolerated.[20]

The combination of pseudoephedrine and domperidone was well tolerated by the patients in this study, as well as by approximately 300 other patients at the clinic who have taken the combination for clinical indications. Some patients did develop irritability and insomnia; these symptoms often disappeared with dose reduction for a time, with gradual reintroduction of the full dose.

Treatment with the pseudoephedrine-domperidone combination caused disappearance of severe snoring and apneas in most patients. Improvement in sleep quality was suggested by the improvement of Epworth scores. Concomitantly, nocturnal oxygen saturations reached or approached normal values in all but four patients, and improvement was maintained as long as the medication was continued. Given the preliminary nature of our observations, neither medication can be recommended for empiric treatment of OSA at this point. Also, patients with gastroesophageal reflux and nasal congestion should continue to be treated using standard parameters of practice. However, in view of the clinical importance of OSA and the need for a simple effective therapy of this disorder, it is hoped that these observations will stimulate interest and further study of this drug combination. In particular, a randomized placebo controlled trial that includes polysomnography and functional status as outcomes, and evaluates each drug separately and in combination is needed to confirm and expand on our observations.

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This was not an industry supported study. Dr. Larrain has financial interests in Faronkal, Ltd., which produces and markets the drug combination of domperidone and pseudoephedrine. The company has the rights to market the drug in Chile and has applied for an international patent. The other authors have indicated no financial conflicts of interest.