



# WILL THERE EVER BE A PILL FOR SLEEP APNEA?

*by Steven Grenard RRT, RPSGT*

Some 25 years ago, in another life, I was assigned to call on a pediatric group home with severely developmentally disabled children who were forever plagued by the inability to handle their secretions, were always congested and at risk of pneumonias. One of the residents was a five year old child who was extremely hyperactive and profoundly retarded. He was literally bouncing off the walls. The only thing that would offer him any rest was either methylphenidate (Ritalin®) or, when that ran out, a shot of Cuban coffee poured into his milk bottle. I was amazed to watch this child take the bottle, suck down a few gulps of the café con leche and then conk out. I thought he died until I examined him more closely and was relieved to find him soundly asleep.

A few years later my wife and I were traveling with her sister, a grown woman, with a serious caffeine addiction. She often sent out for a large cup of black, caffeinated coffee at bedtime and confided in us that she couldn't sleep without it. I chalked this up to the same sort of paradoxical effect methylphenidate and caffeine had in the hyperactive child although she was never diagnosed as hyperactive and didn't appear to be. However, she did drink ten or more cups of java a day which could've kept any symptoms she had in check. Caffeine is a methylxanthine, which is a group of substances that include such drugs as theophylline and aminophylline.

In a 2006 (SLEEP 29[8]:1033) AASM Practice Parameter for the Medical Therapy of Obstructive Apnea there is a brief paragraph which states there are three important publications/studies in the literature which indicate the xanthine drugs have a clinically insignificant effect on reducing the AHI so they are not recommended for this purpose. They add, however, that the recommendation does not cover the possibility of usefulness for central sleep apnea. And apparently, I would add that unless one were hyperactive, such drugs would likely cause insomnia although their possible effect in sleep apnea remains intriguing.

Section 3.2 of the above cited AASM Clinical Practice Parameter discusses four other classes of drugs that have been considered for use in obstructive sleep apnea. These include protriptyline which is not recommended as a "primary" treatment because papers studying this drug back in the 1980s showed no improvement in the AHI or oxygen saturation. This drug suppresses REM, a period where there is apt to be the worst desats and most respiratory events. Along with another REM suppressant, clonidine, these drugs produce improvement because REM is eliminated. The con-

clusion for these drugs is that they showed "mixed" results for the treatment of OSA.

Among the pharmacologic agents studied, estrogen with and without progesterone was also discarded as having either a negative effect on the AHI or a clinically insignificant positive effect. The potential adverse side effects of these hormones also mitigates their use for the treatment of OSA.

Modafinil (Provigil®) was recommended for the treatment of residual daytime sleepiness in OSA patients even with effective PAP treatment if they lack any other identifiable cause for such sleepiness. Such other reasons may include PAP non-compliance, poor mask fit, PAP pressures which are too high or too low, weight gain or loss which impact on PAP pressures that are optimal, poor sleep hygiene, environmental disturbances, and other conditions such as narcolepsy, PLMs and RLS.

But of all the possible medications mentioned for the direct treatment of OSA, the most interesting remain the possibilities that occur with mixed profile serotonin agonist/antagonists. Selective serotonin uptake inhibitors or SSRIs were not recommended in the practice parameter because studies were cited as not leading to "consistent or significant" improvement in the AHI of OSA patients. The hypothesis for not recommending these drugs includes the suggestion that a Only a targeted approach in the design of such drugs would lead to definitive conclusions on their efficacy. The section on these drugs points out there are multiple serotonin receptors and different effects of these drugs occurs on the central or brainstem receptors as opposed to the effects on the peripheral receptors of the upper airway. Among the SSRIs studied were I-tryptophan, fluoxetine and paroxetine which according to researchers have produced some improvement in AHI but only during non-REM sleep. And in some patients these agents have shown no improvement at all in any stage of sleep.

David W. Carley and Miodrag Radulovacki of the University of Illinois at Chicago have been studying one such mixed profile serotonergic agent, an antidepressant known as mirtazapine (Remeron®) for nearly a decade. In 1999 they published the results of an animal study using special rats that are established animal models for central sleep apnea. The animals were wired to diagnose sleep staging and breathing (minute ventilation). The results of these animal studies indicated that mirtazapine reduced the apnea index during NREM



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sleep by more than 50% and during REM by more than 60% for at least 6 hours. The minute ventilation, in association with this apnea suppression, increased during all sleep/wake stages. And NREM Delta sleep increased by more than 30%. They concluded, for the Sprague-Dawley rat at least, that mirtazapine significantly reduced central sleep apnea during REM and NREM sleep. This was in 1999.

In 2003 the announcement made from Carley and Radulovacki was that a human clinical trial at the University of Illinois (Chicago) demonstrated the first promising drug treatment for sleep apnea. According to the data Presented mirtazapine cut in half the number of times breathing ceased (apneas) or decreased (hypopneas) during sleep and reduced the number of times sleep was disrupted (arousals) by 28%. 12 patients who were studied in this group are claimed to have shown improvement. The 12 patients were between ages 12 and 70 and received one of two dosages or a placebo and hour before bedtime and then monitored via polysomnography after each of three seven day treatment periods. In 2004 a group from Santiago, Chile including C Guillemineault, JL Castillo, P Menendez and L Szegovia provided a single published case of an 82 year old male with EDA and loud snoring. His PSG had an AHI of 54.9 and his oxygen saturation dropped to 78%. He had an arousal index of 40.4 arousals per hr. He was titrated onto CPAP to a level of 8 cmH20 but afterwards refused the CPAP as do so many recalcitrant OSA DO. So he was begun on a course of mirtazapine, 15 mgs, at bedtime and was re-tested after three months. His AHI dropped to 9.3 events per hour and his O2 sat improved, marginally, to a low point of 81%. Subjectively he reported a diminution of his EDS, improvement in functioning and no side

effects. The abstract did not indicate whether he adopted a different position on the second study compared to the first. Positional changes can also result in dramatic changes, increases or decreases, in the AHI.

Carley, Radulovacki and colleagues at the University of Illinois also published a 12 person study on mirtazapine in the January, 2007 edition of SLEEP (30[1]:35-41) which demonstrated that daily administration of 4.5 to 15 mgs of mirtazapine for 1 week reduces AHI by half in adult patients with OSA. What makes this drug different from other SSRIs is, they feel, the fact that it is a mixed profile serotonergic. But the anti-climax is that mirtazapine is also associated with sedation and weight gain, two negative effects for people with OSA. OSA patients are often advised to lose weight and such patients not well controlled by PAP therapy exhibit excessive daytime sleepiness which could be exacerbated by the residual effects of this drug. Although these are not insurmountable obstacles to the use of this drug for OSA, the authors found that after a decade of working with this drug they could not recommend it for the treatment of OSA. One suspects this will not be the last we will hear about mixed profile SSRIs. Other formulations and the ways and means of dealing with their side effects as well as their use as adjunctive therapy (they only seem to eliminate about one half of the AHI) is sure to come and the elusive goal of a pill for OSA may yet come to pass.

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