



EFFECTIVENESS OF ZONISAMIDE IN REDUCING SLEEP-DISORDERED BREATHING IN OVERWEIGHT AND OBESE PATIENTS WITH MODERATE-TO-SEVERE OBSTRUCTIVE SLEEP APNOEA: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

The inhibitors of carbonic anhydrase minimise the apnoeic events of the sleep related breathing disturbances disease. There is also the prevention of weight loss as the drug that causes weight loss in the overweight person; the carbons anhydrase which is inhibited by zonisamide. The study was conducted in order to find out in quantitative way relative role of these two features that can be used to reduce obstructive sleep apnoea (OSA). A standard care that was continuous positive airway pressure or CPAP was the tool used to compare the methods. The people on whom this trial was conducted were moderate plus severe OSA conditioned people with a body mass index (BMI) of 27-35 (kg/m²) and were randomly assigned the zonisamide, placebo or the CPAP over a period of 4 weeks. The second (20 weeks) period resulted in comparing the CPAP and zonisamide in the sense of open-label extension study. There were polysomnography, laboratory testing and symptom check. As of the 4th week, zonisamide exhibited even greater decrease in apnoea/hypopnoea index (AHI) by 33 39 % and oxygen desaturation index by 28 31 %. After 24 weeks follow up period, averagely the AHI decreased by 13 percent and 61 percent when using zonisamide and CPAP respectively ($p=0.001$). Thoughts there was little variance in body weight in 4 weeks after which the weight decreased after zonisamide application and was increased after application of CPAP (-2.713.0 vs. 2.320.0, $p0.001$). The level of Bicarbonate decreased after 4 weeks and 24 weeks with Zonisamide. Trends were demonstrated to be on the adverse side in zonisamide. Zonisamide also reduced OSA despite no weight loss and this can be explained by the aspect that zonisamide has the properties of carbonic anhydrase inhibition. Nonetheless, its effect was not as massive as the effect of CPAP on it.

Key words: Carbonic anhydrase, Zonisamide, Obstructive sleep apnoea (OSA), Continuous positive airway pressure (CPAP), Apnoea/hypopnoea index (AHI)

INTRODUCTION

Obstructive sleep apnoea (OSA) is the phenomenon when upper airway is blocked partially or completely resulting in condition with low oxygen and high levels of carbon dioxide and arousal at other rates. Cardiovascular outcomes and metabolic issues characterized by excessive daytime

sleepiness as the main outcomes of OSA and the fact that descending deeper into the matter the results of the study also report the absence of sleep after sleeping, the impaired thinking process and the emotional instability that are accompanied by the results of the cognitive and emotional fragmentation and the emotional instability also present some of the results that condition the development of the outcomes to be presented [1,2] and are included in the results of the study to be cited further. Common form of treatment in OSA involves use of continuous positive airway pressure (CPAP) as still the form of treatment of OSA is yet the gold standard, but is carried out partially on long-term basis with success rate as low as 50 percent of the time [3,4] which is why other or supplemental forms of treatment are sought out now. Among numerous effects of action of zonisamide, it is possible to enumerate inhibition of single and multiple isoenzyme of carbonic anhydrase [5,6]. Even a substitute agent with carbonic anhydrase inhibitory properties (i.e. acetazolamide and topiramate) has been known to suppress central apnoeas in individuals with heart failure and obstructive occurrences in subjects with OSA 10 and 11 and 12. Though it does not have a full comprehension of what really occurs, the change in the acid-base level towards the increased acidity is also believed to lead to an excitement of the respiration activity [7,8] No interaction between zonisamide as weight loss reliever and effects of this product on the respiratory control of individuals with OSA has so far been carried out. The hypothesis we postulate here is, since, the carbonic anhydrase inhibitor action of zonisamide would result in reduction in the apnoeic events of the overweight / obese patients with OSA. Pharmacological effect comprises the direct influence on the breathing in relation to carbonic anhydrase inhibition and the secondary effect developed by the weight loss. We also could compare the outcome when we used CPAP along with the use of zonisamide when it comes to compliance of the patient as far as the overall therapeutic outcome is concerned.

METHODS

Subjects

The Department of Sleep Medicine, at Sahlgrenska University Hospital in Gothenburg, Sweden, screened 715 patients with OSA, who were prescribed to use CPAP, in akin conditions, including: 1 AHI of above 15 events/h-1, 2 body mass index (BMI) of 27-35 kg/m² and 3 Epworth Sleepiness Scale (ESS) of more than 6. The patients having the past history of seizure diseases, unstable cardiovascular, pulmonary and gastrointestinal disease process, depression, substance abuse, and drugs interfered with protocol of the study were also excluded. There was also the danger of occupational loss, since it led to the risk of sleepiness and significant nocturnal hypoxaemia (at least 10 incidences and the saturation of oxygen in arteries at pulse oximetry (SpO₂) was lower than 50 per cent or failure to resaturate adequately) which these patients were not allowed. Among 70 potentially possible participants, 50 (18-75 years) individuals consented to take part in the research. The Ethics Committee of the University of Gothenburg had passed the protocol (697-09). All the participants conducting the researches were required to give informed assent.

Study Design and Procedure

It was a second, a three-arm, a parallel, placebo-controlled, randomized, and a double-blind in an open extension part. After 4 weeks of therapy each of the participants were randomly assigned either to zonisamide, placebo or CPAP in an order list (randomization list (block randomization (n=6); drug A or B, C = CPAP) by the independent Apoteket Production och Laboratorier (Stockholm, Sweden). A third party also was undertaking monitoring of study process and adherence to the protocols in the university hospital. After the phase of open extension (20 weeks), all other subjects (those, who were not prescribed to have CPAP) were treated with zonisamide. Follow-up of these subjects was done after 4 and 24 weeks, using in the sequence, sleep surveys, blood pressures, blood samples, questionnaires (ESS [9,10], Fatigue Impact Scale (FIS) [11], Zung self-rating depression [12, 13] and anxiety [14,15]) questionnaires, and anthropometrics and body fat distribution. Patients were titrated according to the respective step protocol (100 mg / week per administration of

zonisamide 100 mg zonegran; Eisai Limited, Hatfield, UK) or pla TiV was carried out till the maximum dose (300 mg / day) was reached. At the side effects level, at reduction in dose (100-mg steps) may be adopted to be treated as it pleases the investigator. Being a piece of advice concerning the time to be administered the medication, it should be at the time between 20.00 h and 22.00 h. The adherence to the study drug and placebo was determined by number of tablet intake. There was no weight counseling in this research.

Sleep Studies

The ambulatory polysomnography (PSG) sleep study held at home, based on the standard protocol, was used to measure the sleeping [16,17]. Two ambulatory PSGs, which were full-night polysomnography, were carried out as a baseline (Embla A10 system; Flaga, Reykjavik, Iceland). This was done by analyzing the data on the second PSG night (it can not be the first PSG habituation night). To be followed by this, the patients were measured at nights in weeks 4 and 24, respectively about PSG. The PSG comprised of electro-encephalograms (C3- A2, C4- A1, Fz- A2 and Oz- A1), left/ right electrooculogram, electromyogram chin, right/ left tibialis, ECG, nasal cannula and oronasal thermistor and respiratory thoracic/ abdominal move. The body position and oxygen saturation. The PSG recordings became manually carried out whereas an experienced scorer was blind to the treatment allocation on produces of the American Academy of Sleep Medicine [18]. The occurrence of the events of Apnoea was described as a decrease by 90% or more through removal of at least 10 s of baseline airflow signal. Hypopnoea was made up of a reduction of the base of airflow signal of half or more and also by ten seconds or more or by a desaturation of three per cent or more as well as by the or one arousal. They were repeated as the number of apnoeas and hypopnoeas per an hour of sleep and converted into AHI. The number of the total number of 4 and more oxygen desaturations of each hour of sleep during a single hour of sleep formed the grounds on which oxygen desaturation index (ODI) was calculated. The means and the minimum SpO₂ along with the time spent <90%SpO₂ (T<90%sat)) during the process of recording sleep knowledge were calculated. A single member of the placebo group could not be analyzed because of low PSG recordings in the course of the week 4.

Analysis

Sample Size Estimation

It was also classified as a sample where the past in-house reports of the studies of OSA treatment were made; as a basis, the reduction of the AHI was presumed against the placebo by the mean of $7.5 \pm \text{sd } 6$ events h⁻¹. Parallel-group design with 30 patients in each of the two arms would enable a power of 90 percent to detect a significant difference between treatment groups (two-tailed p0.05).

Efficacy Variables

The most important discovery of the research was the role of the efficacy of the pharmacological weight loss in OSA in evaluation of the effect of AHI as a central measure. Also, there was a study of 24 weeks of sleep apnoea alleviation (SAA). The second efficacy outcomes corresponded to the difference in AHI and ODI after four weeks in the blinded section of the protocol between placebo and zonisamide. Other secondary efficacy variables involved and comprised of the mean SpO₂, minimum SpO₂ and time and spent T<90%sat; PSG-derived sleep variables, total sleep, proportion of sleep stages, and anthropometric variables of weight, BMI, body fat distribution, blood pressure and the questionnaire values of week 4 and week 24. A placebo-adjusted percentage change was assumed to be a difference between the active and the placebo arm of the treatment.

Sleep Apnoea Alleviation

CPAP versus drug: the outcomes of the treatment interventions of CPAP were compared against the outcome of the drug with the correction of absolute intake of CPAP (adjusted to habitual sleep time) on the 24-week duration of the treatment regimen [3]. The former is the identification of the level of effectiveness of CPAP intervention in the discipline of AHI or ODI which was estimated in

relation to the baseline value. The meter-read that depicted CPAP adherence was matched to the usual sleeping time that was reported by the individual. Then a measure of the efficacy of the treatment (SAA) was computed. By doing so, the success of treatment of the patient who had their AHI decreased by half, i.e., 50 events h⁻¹ to 10 events h⁻¹, would thus be 80 percent. In view of the fact that the CPAP meter may record an average of 6hours of usages a night and the consumption of sleep was of 8hours of sleep a night, the percentage coverage of the alleviation of the treatment would be 75 percent. In the case patient, SAA would be 80 per cent times 75 or 60. The urge behind the choice of SAA was to present a justifiable comparison between the two categories, i.e. mechanical and pharmacological routes of treatment, as far as elimination of sleep apnoea is concerned in terms of absolute value. Thus, the effectiveness of the drug therapy group was identified. In the case where assumption of the patient after the therapy using the drugs was taken, the users time would be the same as the habitual time to sleep and efficiency parameter would be SAA. The analysis failed to include four patients (non-acceptors) who refused to proceed to the treatment using the CPAP machine.

RESULTS

Table 1 – Baseline Characteristics

Parameter	Placebo	Zonisamide	CPAP
Subjects	33	33	34
Males/females	28/5	30/3	29/5
Age (years)	54±12	56±9	45±8
Treated hypertension (%)	48	42	16
BMI (kg·m ⁻²)	32±3	32±3	32±3
Waist/hip ratio	1.00±0.07	1.04±0.11*	1.02±0.08
Neck circumference (cm)	44±3	45±3	45±4
Systolic BP (mmHg)	138±18	142±15	133±18
Diastolic BP (mmHg)	85±9	85±11	84±8
Heart rate (beats·min ⁻¹)	60±11	60±8	67±7#¶
AHI (events·h ⁻¹)	51±24	43±25	49±27
ODI (events·h ⁻¹)	44±22	36±22	45±26
ESS score	13±5	14±6	15±5

Table 2 – Effects of Placebo and Zonisamide on Sleep Apnoea and Sleep-Related Variables at 4 Weeks

Parameter	Placebo	Zonisamide	p-value
Subjects (n)	33	33	
AHI (events·h ⁻¹)	2.5 (-3.1–9.2)	-7.8 (-15.4– -1.3)	0.03
ODI (events·h ⁻¹)	-1.2 (-5.1–3.7)	-8.3 (-14.1– -2.5)	0.02
CAI (events·h ⁻¹)	0.1 (-1.0–1.5)	0.1 (0.0–0.3)	ns
Apnoea index (events·h ⁻¹)	0.0 (-4.5–4.3)	-2.2 (-9.5–4.1)	ns
Hypopnoea index (events·h ⁻¹)	5.8 (1.2–10.2)	-4.7 (-9.8– -0.3)	<0.01
Apnoea duration (s)	0.2 (-2.8–3.2)	0.0 (-3.4–3.5)	ns
Arousal index (events·h ⁻¹)	3.5 (-2.4–9.0)	-6.4 (-13.2–0.5)	0.01
Mean SpO ₂ (%)	0.02 (-0.65–0.68)	1.23 (0.14–2.15)	0.03
Minimum SpO ₂ (%)	0.5 (-1.8–3.0)	1.1 (-2.1–4.0)	ns
T<90%Sat (%)	-1.2 (-6.5–3.0)	-6.8 (-14.0–0.3)	ns
TST (h)	-0.2 (-0.8–0.6)	0.1 (-0.6–0.7)	ns
Sleep efficiency (%)	-4.8 (-9.6–0.5)	-0.3 (-4.1–3.5)	ns
Stage R (% of TST)	-1.5 (-4.2–1.0)	-0.9 (-5.0–3.5)	ns
Stage N3 (% of TST)	-1.0 (-4.0–2.5)	0.5 (-2.9–3.8)	ns

The table 1 shows demographic characteristics of three groups that were a part of a treatment, such as placebo, zonisamide, and CPAP. The study examined a total of 34 participants in the CPAP group and 33 participants were asked to join in the zonisamide and the placebo group. The proportion of genders was very balanced with the males and females with the exception that a small percentage of the male people were in excess among a given population. Participants of placebo group and zonisamide were 54.12 years old and 56.9 years respectively and CPAP group younger at the age of 45.8 years old. In the placebo and the zonisamide groups, 48 percent and 42 percent respectively were found to have been occurring hypertension as compared to the sixteen percent that was found to have occurred in the CPAP group. The body mass index (BMI) was the same in all the three groups, 32.3 kg/m². The risk of having the waist to hips ratio indicates that the zonisamide group had a higher rate compared to the placebo and the CPAP group and the outcome was significant. Other parameters of an estimation line including the neck circumference, the systolic blood pressure, the diastolic blood pressure and the heart rate were also the same and similar between the groups except that the heart rate was high in the CPAP group. According to Table 2, the result shows the effect of placebo and zonisamide in sleep apnoea and sleep variables at 4 weeks. The intervention of zonisamide was associated with the relevant improvement of the index of apnoea / hypopnoea (AHI) and index of oxygen saturation abatement (ODI) than in the case of placebo (-7.8 events / h and -8.3 events / h respectively p 0.03 and p 0.02). Line significant reduction of hypopnoea index also occurred with zonisamide use as well; the value was -4.7 events h⁻¹ with increased 5.8 events h⁻¹ in the placebo group (p < 0.01). An additional parameter of sleep fragmentation, sleep peak, was also improved with zonisamide, which indicated -6.4 events h⁻¹ improvement compared to that of placebo that recorded only an increase (p = 0.01). Besides, the mean SpO₂ level was also significant in the improvement of the group that used zonisamide (p=0.03), although the other signs of sleep, including the minimum SpO₂, T<90 percent saturation, total sleep time (TST), sleep efficiency, and sleep stages did not indicate the difference between two groups was important. These results refer to zonisamide as a potential positive by-product of sleep apnoea severity and quality of sleep, especially on the decrease of the number of hypopnoeic events and the subsequent increase in oxygenation.

DISCUSSION

The given randomized controlled trial is the first one to indicate that zonisamide was able to enhance breathing and oxygenation of the overweight and obese people with the moderate-to-severe OSA. It was highly fluctuated, regardless of an initial weight of an individual prior to the experiment, and extended to even 6 months. The advantage of the increased quality of night breathing happens to be there, but a decrease of daytime sleepiness cannot be observed. The modifications, which were made relating to the compliance, could not be compared with the effect that it acquired with the intervention of CPAP. The application of the carbonic anhydrase inhibition in treating the sleep-disorder breathing is not a new idea. The type of enzyme that has been discovered to be characteristically distributed in the body as well as the kind that promotes contributions by a large margin when it comes to body excretion of carbon dioxide is the carbonic anhydrase [19]. Carbonic anhydrase is also inhibited in the kidneys leading to the occurrence of metabolic type of acidosis that aided the ventilation (along with the aid of chemosensors) [20]. The carbonic anhydrase inhibitors also help in the ventilation and a little bit in inhibition of carbonic anhydrase in the tissues in the red cells [21]. High-altitude periodic breathing [21], central apnoea of CheyneStokes type [10] and OSA [11], [22] have also been treated with carbonic anhydrase inhibitors, e.g. Acetazolamide. The inhibition of sodium channels and 2-aminobutyric acid are some of the effects that the zonisamide has on the carbonic anhydrase as other effects are also reported [23]. The issue here is whether the impact on findings of this study has been affected by the effects or not. A study of acetazolamide OSA conducted long ago indicated that there existed direct correlation between the degree of bicarbonate change and the diminution of the apnoeic events. Nevertheless, although the level of bicarbonates altered in the process of this study with the help of zonisamide, a direct

relationship between a low bicarbonate level and an improved OSA was not obtained. The implicated physiology of responsiveness in the patient remains inatured, yet can be attributed to matters in terms of the presence of an upper airway collapsibility, the so-called chemosensory capacity, arousal depth or even an alternate hereditary composition. Recent findings on the current effort to conduct a classification of OSA patients report that in an estimated, one third of the latter, the respiratory control mechanisms can be manipulated. Acetazolamide reduced loop gain, and the AHI by the same amount in patients with moderate to severe OSA, in a case control review. This type of effect can be made on zonisamide whereby decrease in the AHI could only be achieved by a pool of selected people and not Nyx. Further experimentation into the process of doing so in the determination of the patients with high loop gain will perhaps reveal an even more significant role in the zonisamide of treating the OSA. OSA has also proved to correlate with obesity closely and the implication of this is that a patient with OSA can be made better by losing weight. The study of Zonisamide is based on the basis of reducing weight. A study of randomized-controlled trial carried out over 11 years period of time has conclusively arrived at a conclusion that 400mg of zonisamide reduced weight further among obese patients who were on a lifestyle and diet program [8]. Nonetheless, in the trial the role of zonisamide on the elimination of the sleep disordered breathing was not explored. Recent trial of the topiramate which has the carbonic anhydrase inhibitory effect combination with phentermine showed it to have most noteworthy enhancement of sleep apnoea and also had positive correlation impact of the its effect on weight loss in obese patients with OSA [12]. We saw OSA effect in this study but in the study in which we used 300 mg zonisamide daily and did not use weight counseling in it, there is stronger possibility that no weight loss effect will be observed and this is a possible reason in the case of the OSA effect that we obtained, unless perhaps more than the relaxing effects of the carbonic anhydrase inhibitory effects. Interestingly, overall effects of zonisamide on OSA were minimal and can only be considered to be clinically important in a subset population of the patients as it indicates in figure 2a. But evidently in the small sample, all the treatment response predictors failed to appear. It also has a potential that the weight counseling and zonisamide in patients with obstructive hypopnea also have the potential to bring the improvement of the treatment plans. One of the outcomes that were given in this paper is the improvement of apnoeas. It came up with a finding that CPAP, though standardized in OSA resolution remains to be better than zonisamide though also standardized. Only in CPAP, daytime sleepiness was enhanced. The outcome was the reduction of zonisamide and zonisamide and CPAP treatment to favorable body composition measures, and massive weight gain (2.3 kg) at every 24 weeks. In the patients of OSA, the cause of CPAP weight gain remains unraveled yet the belief has been that the same might be related to the changes of leptin and emergence of insulin resistance among the obese OSA subjects. As compared to the zonisamide group, a large number of side effects that were mostly minor however did occur and the rate at which the study was dropped out in the patients using zonisamide was equal to that of the patients in the CPAP group. The pluses should be mentioned when it seems that the CPAP is perceived in a favorable way, nevertheless, it should be stated that the results of the zonisamide were heterogeneous and a part of the patients were allergic to the pharmacological treatment.

It was a placebo-controlled and randomized trial with early assessment of the impact of zonisamide on sleep-related breathing, extension study, which is independent of analysis of significant changes of body composition. It was also able to establish even though straight or long term zonisamide versus CPAP with adjustment on compliance treatment of OSA. The limitations of the research also contain the failure to obtain the desired sample of the patients who participated in the research because the sample could not be easily reached but the desired hypothesis was confirmed using the available targets. Analysis of the results of the use of zonisamide in unselected patients with OSA without the aim of maximizing their weight loss and detection of some phenotypic peculiarities of the population is an issue of concern to the authors of this study. The research was random, although younger baseline level occurred in the CPAP group as compared with zonisamide group. The side symptom of dysphoria was reported after the prior one at 24 weeks and they declare that 20 per cent

of zonisamide patients underwent this side symptom, but on comparison with placebo they found no effect on the side symptom in 4 weeks. According to ESS scores, the somnolence was not improved in zonisamide group despite the fact that somnolence is a common side effect of zonisamide drug. The ability of zonisamide to reduce OSA should be examined as to whether it negated the effects of somnolence or not. Finally, this research showed that zonisamide carbonic anhydrase inhibitor enhanced sleep-disordered breathing among the patients with OSA. Even after correction on basis of compliance the global outcome was lower than CPAP outcome. The findings of the present study do not promote un-selective use of zonisamide in patients with OSA but the findings indicate that carbonic anhydrase can prove to be an effective target in the spectrum of further studies on the pathophysiology of OSA and sequelae (hypertension). We would appreciate to express our gratitude to Ann-Christin Lundquist (Center of Sleep and Vigilance Disorders, Department of Internal Medicine and Clinical Nutrition, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden) who developed the study to the authors.

CONCLUSION

Conclusively, this study offers evidence that zonisamide which is a blocker of carbonic anhydrase is able to decrease sleeping-disordered- breathing in the more than 25%-overweight and the obese victims who have usually moderate-severe obstructive sleeping- apnoea (OSA). The difference in the treatment effect was significant; it was not, however, significant to the level it was in continuous positive airway pressure (CPAP) therapy even after the adherence had been corrected. The information shows that the potential medical impact of zonisamide can be connected with the impact on carbonic anhydrase inhibition, and, thus, the effect of weight loss is played not quite such an important role being absent the weight suggestion in the study. As per its promise, the impact of zonisamide was separated and in patients, there was partial manifestation of a miscellaneous response in their OSA. The research also showed that nothing came better than CPAP treatment, as far as treatment of sleep apnoea and shrinking down on the sleepiness during the day was concerned. With these findings in mind, it is not clearly instant that zonisamide must be employed in widespread in the avulsions of unselected OSA patients although it seems as though its mode of working is being brought to bear in a dissimilar mode with those prescription drugs explicitly in the treatment of OSA patients precisely by resorting to commodities such as hypertension. Further studies to investigate phenotyping the patients and employing them in weight loss in future may assist in cashing in on the clinical potential that zonisamide can offer in the treatment of OSA.

REFERENCES

1. WT McNicholas MR Bonsignore Management Committee of EU COST ACTION B26 Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J* 2007; 29: 156–178.
2. MR Bonsignore C Esquinas A Barceló . Metabolic syndrome, insulin resistance and sleepiness in real-life obstructive sleep apnoea. *Eur Respir J* 2012; 39: 1136–1143.
3. L Grote J Hedner R Grunstein . Therapy with nCPAP: incomplete elimination of Sleep Related Breathing Disorder. *Eur Respir J* 2000; 16: 921–927.
4. WJ Randerath . Alternatives to positive airway pressure for obstructive sleep apnea syndrome. *Expert Rev Respir Med* 2009; 3: 255–263.
5. J Hedner L Grote D Zou . Pharmacological treatment of sleep apnea: current situation and future strategies. *Sleep Med Rev* 2008; 12: 33–47.
6. DH Peters EM Sorkin . Zonisamide. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy. *Drugs* 1993; 45: 760–787.
7. KM Gadde DM Franciscy HR Wagner 2nd . Zonisamide for weight loss in obese adults: a randomized controlled trial. *JAMA* 2003; 289: 1820–1825.
8. KM Gadde MF Kopping HR Wagner 2nd . Zonisamide for weight reduction in obese adults: a 1-year randomized controlled trial. *Arch Intern Med* 2012; 172: 1557–1564.

9. CT Supuran A Di Fiore G De Simone . Carbonic anhydrase inhibitors as emerging drugs for the treatment of obesity. *Expert Opin Emerg Drugs* 2008; 13: 383–392.
10. S Javaheri . Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. *Am J Respir Crit Care Med* 2006; 173: 234–237.
11. H Tojima F Kunitomo H Kimura . Effects of acetazolamide in patients with the sleep apnoea syndrome. *Thorax* 1988; 43: 113–119.
12. DH Winslow CH Bowden KP DiDonato. A randomized double-blind, placebo-controlled study of an oral, extended-release formulation of phentermine/topiramate for the treatment of obstructive sleep apnea in obese adults. *Sleep* 2012; 35: 1529–1539.
13. MW Johns . A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540–545.
14. JD Fisk PG Ritvo L Ross . Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis* 1994; 18 Suppl. 1:S79–S83.
15. WW Zung . A self-rating depression scale. *Arch Gen Psychiatry* 1965; 12: 63–70.
16. WW Zung . A rating instrument for anxiety disorders. *Psychosomatics* 1971; 12: 371–379.
17. D Zou L Grote Y Peker . Validation a portable monitoring device for sleep apnea diagnosis in a population based cohort using synchronized home polysomnography. *Sleep* 2006; 29: 367–374.
18. C Iber S Ancoli-Israel AL Chesson . The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, American Academy of Sleep Medicine 2007.
19. TH Maren . Carbonic anhydrase: chemistry, physiology, and inhibition. *Physiol Rev* 1967; 47: 595–781. ER Swenson KL Leatham RC Roach . Renal carbonic anhydrase inhibition reduces high altitude sleep periodic breathing. *Respir Physiol* 1991; 86: 333–343.
20. CK Grissom RC Roach FH Sarnquist . Acetazolamide in the treatment of acute mountain sickness: clinical efficacy and effect on gas exchange. *Ann Intern Med* 1992; 116: 461–465.
21. KF Whyte GA Gould MA Airlie . Role of protriptyline and acetazolamide in the sleep apnea/hypopnea syndrome. *Sleep* 1988; 11: 463–472.
22. DM Rock RL Macdonald CP Taylor . Blockade of sustained repetitive action potentials in cultured spinal cord neurons by zonisamide (AD 810, CI 912), a novel anticonvulsant. *Epilepsy Res* 1989; 3: 138–143.
23. Y Ueda T Doi J Tokumaru . Effect of zonisamide on molecular regulation of glutamate and GABA transporter proteins during epileptogenesis in rats with hippocampal seizures. *Brain Res Mol Brain Res* 2003; 116: 1–6.
24. Y Masuda T Karasawa . Inhibitory effect of zonisamide on human carbonic anhydrase in vitro. *Arzneimittelforschung* 1993; 43: 416–418.