

## SERUM PROGESTERONE LEVELS AND SLEEP HABITS IN PREMENOPAUSAL AND POSTMENOPAUSAL FEMALES

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### ABSTRACT

**OBJECTIVES:** To evaluate the sleep habits in pre and postmenopausal females and to find out the relationship between serum progesterone levels and sleep habits.

**STUDY DESIGN:** Cross sectional study.

**PLACE & DURATION:** At Islamic International Medical College Rawalpindi from 1<sup>st</sup> March 2010 to 31<sup>st</sup> March 2011.

**METHODOLOGY:** A total of 60 females were randomly selected out of which 30 were premenopausal (Group A) and 30 were postmenopausal (Group B) females. The sleep habits were assessed by sleep questionnaire and blood sample was taken for serum progesterone levels and were analyzed by enzyme-linked fluorescent immunoassay (ELFA) technique.

**RESULTS:** The comparison between pre and postmenopausal females was done on the basis of their sleep habits and statistically significant results were found which showed that postmenopausal females had lesser sleep duration than premenopausal females ( $p=0.011$ ). Postmenopausal females had more frequency of nocturnal arousals than premenopausal females ( $p<0.01$ ), postmenopausal females awoke in morning without an alarm while most of the premenopausal females needed an alarm to wake up ( $p=0.000$ ) and postmenopausal females woke up earlier in the morning than premenopausal females ( $p=0.000$ ). Serum progesterone levels of postmenopausal females were lower than premenopausal females ( $p=0.000$ ).

**CONCLUSIONS:** Serum progesterone levels affect the sleep pattern of females across the menstrual cycle and menopause. As the serum progesterone levels decline after menopause; the sleep habits of females get affected and have relatively poor sleep quality, more evening tiredness and more dream remembrance as compared to premenopausal females.

**KEY WORDS:** Sleep habits, Progesterone, Menopause, Hormone Replacement Therapy.

### INTRODUCTION

Sleep is a state of unconsciousness in which the brain is relatively more responsive to internal than external stimuli<sup>1</sup>. Sleep is a homeostatically regulated process, without revitalizing forces of which survival might not be feasible. People spend about one-third of their lifespan in sleep<sup>2</sup>. In adults a daily sleep of 7 to 8.5 hrs is considered to be effective<sup>3</sup>. Sleep is a combination of Rapid Eye Movement (REM) sleep and non rapid eye movement (NREM) sleep. NREM sleep is subdivided into four stages numbered as stages 1-4, which are consistent with increasing depth of sleep<sup>4</sup>. Stage 3 and 4 are often grouped together under the label "Slow Wave Sleep" (restful sleep). In REM sleep; the brain is mostly awake and dreaming occurs which is usually remembered by most persons<sup>5</sup>. Sleep disorders are common, and at least 10% of the population suffers from a sleep disorder that is clinically significant and of public health importance<sup>6</sup>. Several community based surveys of sleep disturbances have demonstrated that sleep disturbances and prevalence of insomnia increases with age, especially among women<sup>7</sup>.

Changes in hormonal levels (estrogen & progesterone) across

the menstrual cycle and during menopause in females strongly influence their sleep habits and may cause sleep disturbances<sup>8,9</sup>. Progesterone has direct sedative qualities via stimulating the production of gamma amino butyric acid (GABA) receptors. It causes hypnosis and increases NREM sleep when administered in young men<sup>10</sup>. It is found that REM sleep is lowest during the luteal phase (LP), which may be associated with the raised progesterone levels. In mid luteal phase; NREM sleep is increased as compared to follicular phase (FP)<sup>8, 11</sup>. The most common menstrual cycle related changes observed in sleep habits of healthy females are reduction of REM sleep in luteal phase and more slow wave sleep<sup>12</sup>. During the late luteal phase, a two-fold increase in the number of nocturnal arousals occurs<sup>13</sup>. Disturbed sleep and increase in frequency of REM sleep occurs during late luteal phase and premenstrual period. Longer sleep onset latency (SOL) and poor sleep quality also occurs during the late luteal (low progesterone) phase<sup>14</sup>.

A female preponderance in the prevalence of self-reported sleep problems is evident by midlife<sup>15</sup>. By the time a woman approaches menopause in late 40s; her ovaries begin to shut down, producing less estrogen and progesterone. Postmenopausal females tend to report sleep disturbances twice as commonly as premenopausal females. Sleep difficulty is one of the hallmarks of menopause. One fourth to one half of all women will note some sleep complaint during menopause as compared to approximately 15% of the general population. In a study of pre and postmenopausal women with depression and matched controls, a decrease in SWS and an increase in REMS frequency were observed in post- but not in premenopausal women<sup>16</sup>.

Sleep disruptions are common in women, with reports of insomnia occurring 1.5–2 times more frequently than in men.

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Thus, sleep disorders and insomnia are major features of the medical care of women during menopause and should be appropriately addressed by physicians who treat these women<sup>17</sup>. Both age and hormonal changes can contribute to disturbed sleep habits in middle-aged women undergoing the menopausal transition<sup>18</sup>. Very few studies have objectively characterized the effects of progesterone administration on sleep although preclinical studies have shown that certain neuroactive progesterone metabolites produce sedative-like effects<sup>19</sup>. Hormone replacement therapy (progesterone or both estradiol & progesterone) can improve sleep quality in postmenopausal women under baseline conditions by increasing slow wave sleep and decreasing the frequency of nocturnal arousals<sup>20,21</sup>.

Hormone replacement therapy (HRT) also has positive effects on sleep in women after menopause and causes reduction in insomnia, improvement in falling asleep, diminished nocturnal restlessness, and fewer awakenings, normalising the distribution of SWS in menopausal women, leading to a pattern resembling that of younger subjects and reduced intermittent wakefulness<sup>22</sup>.

The *objectives* of this study were to evaluate the sleep habits in premenopausal and post menopausal females and to find out the relationship between serum progesterone levels and sleep habits.

## METHODOLOGY

The study was conducted in the Department of Physiology Islamic International Medical College, Rawalpindi. Premenopausal females were selected from Islamic International Medical College Rawalpindi and the postmenopausal females were selected from Rawalpindi Cantt and KRL colony Islamabad. The study was completed in 1 year and one month (1<sup>st</sup> March 2010- 31<sup>st</sup> March 2011). Ethical approval was given by the ethical review committee of Riphah international University Islamabad. It was a randomized cross sectional study. The subjects were divided into two groups (A and B). Each Group A (n1=30) included premenopausal females in the age range between 18yrs to 24 yrs, having normal onset of menarche, well developed secondary sex characteristics, regular menstrual cycles. Group B (n2=30) included postmenopausal females in the age range between 40 years to 65 years were included. They had natural onset of menopause, no postmenopausal bleeding and were apparently healthy. All females were divided into three categories on the basis of their serum progesterone levels. Category 1 included those females whose serum progesterone levels were less than 0.5ng/ml and this level matched the post menopausal status. Category 2 included females whose serum progesterone levels were more than 0.5ng/ml and less than 0.8 ng/ml and these levels match the levels in early follicular phase. Females whose serum progesterone levels were > 0.8 ng/ml were included in category 3 and these levels corresponded luteal phase.

The subjects who were on sedatives, anxiolytics, anti depressants, anti convulsants, steroids or hormonal replacement therapy were excluded from the study. Also the

subjects with history of irregular menstrual cycle, polycystic ovarian disease or any surgery in recent past were excluded from the study. The serum Progesterone levels of all the females were measured. Written consent was taken from the participants. Sleep questionnaire was filled by interviewing the subjects in which the sleep time, awaking time, sleep duration, mode of awakening, number of awakenings per night, dreams memory, napping frequency, morning and evening tiredness was assessed. Blood sampling through phlebotomy was done. The pulse, temperature, blood pressure of all the subjects was noted at the time of sampling. The premenopausal females were also asked about the date of their last menstrual period (LMP) to know the phase of their menstrual cycle. The samples were coded and sent to laboratory for serum progesterone levels evaluation by enzyme-linked fluorescent immunoassay (ELFA) performed in an automated VIDAS instrument.

Data was analyzed using SPSS 17 and comparison between the sleep habits and serum progesterone levels of premenopausal and postmenopausal females (Category 1, 2 & 3) were assessed by applying analysis of variants (ANOVA). p value less than 0.05 was taken as significant. The sleep habits of two groups (Group A & B) were analyzed by student's t-test. Analysis of more than two groups was done by using ANOVA. Mean, Standard Error of Mean, F and p values were evaluated by using Benefferoni. The percentage and number of females was found out by using cross tabs.

## RESULTS

Table I illustrates the comparison between the serum progesterone levels and sleep habits in two groups of females. Groups were labeled as A and B. Group n1 included 30 premenopausal females and group n2 included 30 post menopausal females. The mean progesterone levels in nanograms per milliliter (ng/ml) were evaluated and the sleep habits of the females in two groups were compared by assessing their time to go to bed at night, number of awakenings from sleep per night, total duration of sleep in hours, their daily wake up time and mode of awakening in the morning. Mean value of each variable was taken out for each group and value of Standard Error of Mean (SEM) was calculated. The mean value of one group for each variable was then compared with the mean value of that of the other. p value was calculated by applying t test and value <0.05 was taken as significant. The p value for progesterone level between two groups was 0.001 showing statistically significant difference. The serum progesterone levels of postmenopausal females were lower than that of premenopausal females. The comparison between two groups on the basis of number of awakenings during sleep per night was statistically significant with p value 0.000, showing that the postmenopausal females had more frequency of nocturnal awakenings than that of premenopausal females. The p value for comparison of total sleep duration of n1 and n2 was 0.011 which was also statistically significant showing that sleep duration of pre and post menopausal females was different and the duration of sleep was less in post menopausal females as compared to pre menopausal females. The p value for

comparison of wakeup time of n1 and n2 was 0.000 which again was statistically significant. The post menopausal females awoke earlier in the morning than the pre menopausal females. About mode of awakening, out of 30 premenopausal females (n1), 22 (73.3%) needed alarm to get up and 8 (26.7%) females did not need alarm and they woke up without alarm. All the 30 postmenopausal females (n2)(100%) woke up without alarm in the morning. The p value was taken out by applying t test and was found highly significant.

Table II depicts the comparison between two groups of females on the basis of their daytime sleepiness. The sleep habits of the females in two groups were compared by assessing their feelings within first 30 minutes after awakening in morning, number of napping per week, feeling of tiredness in evening. p value was calculated by applying t test and value <0.05 was taken as significant. Feeling within first 30 minutes after awakening in morning was further divided into four categories. Category 1 included those subjects who were alert in the morning, category 2 included those who were somewhat drowsy but alert, category 3 comprised those subjects who felt very drowsy and category 4 comprised those subjects who felt groggy. It was found that 20 (66.7%) out of 30 pre menopausal females were alert in the morning and the rest (33.3%) felt somewhat drowsy but were alert. In comparison 11 (36.7%) postmenopausal women were drowsy, 10 (33.3%) were somewhat drowsy but were alert, 6 (20%) were groggy and only 3 (10%) were alert in the morning. The comparison of the two groups showed statistically significant results with a p value of 0.000 showing that the postmenopausal females felt drowsier just after awakening in the morning than the premenopausal females. The frequency of naps were assessed by asking whether the subjects took nap less than 3 times per week or more than 3 per week or they never took naps or they took nap daily. It was found that 16 (53.3%) premenopausal females took naps daily, 7 (23.3%) took nap more than 3 days in a week, 4 (13.3%) less than 3 times a week while 3(10%) females reported that they never took nap while 14(46.7%) postmenopausal females took naps daily, 11(36.7%) took nap less than 3 times a week, 4 (13.3%) said that they never took nap and only 1 (3.3%) took nap more than 3 times in a week. The comparison between the two groups did not show statistically significant results with p value 0.204, showing that the napping frequency of females of two groups were almost same. Feeling of tiredness in evening was assessed by asking whether tiredness was present or not. During evaluation it was found that 26 (86.7%) premenopausal females said that they had no evening tiredness and only 4 (33.3%) reported that they had evening tiredness while all the postmenopausal women (100%) had feeling of evening tiredness. The comparison of the two groups was significant statistically with a p value of 0.000 which showed that evening tiredness was more common feature in postmenopausal than that of premenopausal females.

Figure I represents the relationship of serum Progesterone levels with the number of awakenings from sleep per night of females included in the study. The percentage of the females is plotted against Y-axis while x-axis represents serum progesterone levels in nanograms per milliliter (ng/ml) of

blood. The progesterone levels of all the 60 females have been divided into three categories which were labeled as 1, 2 and 3. Category 1 included those females whose serum progesterone levels were less than 0.5ng/ml, category 2 included the females with progesterone levels ranging from 0.5ng/ml to 0.8ng/ml and the last category 3 included all those females whose serum progesterone levels are > 0.8ng/ml. A total of 15 females out of 60 falls in category 1, category 2 included 20 out of 60 females and the category 3 included 25 out of 60 females. All the females in category 1 were postmenopausal, while category 2 includes 15 post menopausal and 5 premenopausal females and all the 25 females in category 3 were premenopausal. The colored bars of figure signify the frequency i.e number of awakenings during sleep every night. Blue bar represents the percentage of total candidates who never awoke from sleep during night. Pink bars show the percentage of females who woke up 1 to 2 times at night while asleep. Grey bar represents the percentage of females who woke up 3 to 4 times at night during sleep. Out of 15 females in category 1; 1 female (6.7%) never woke up at night, 4 females (26.7%) woke up 1 to 2 times and 10 females (66.7%) woke up 3 to 4 times at night. From category 2; 2 females (10%) never woke up at night, 9 females (45%) woke up 1 to 2 times and 9 females (45%) woke up 3 to 4 times from sleep at night. Out of 25 females in category 3; 17 females (68%) never woke up at night during sleep, 5 females (20%) awoke 1 to 2 times and only 3 females (8%) woke up 3 to 4 times while asleep at night. The comparison between categories 1, 2 and 3 was done by applying Post Hoc test and mean difference (p value) was taken out. The mean difference value of category 1 and 2 is 0.961 (p1), that of category 2 and 3 was 0.001 (p2) and the mean difference value of category 3 and 1 was 0.000 (p3). This showed that the females of category 1 and 2 had increased frequency of awaking from sleep at night as compared to that of group 3 and the females of group 1 and 2 had almost same frequency of awakening at night.

Figure II represents the relationship of serum Progesterone levels and the number of dreams remembered in a week. X axis represents the three categories of serum progesterone levels and Y axis represents the percentage of females. A total of 60 females were grouped in 3 progesterone categories. The bars represent the number of dreams remembered in a week. The blue bar represents the percentage of females who remembered dreams only rarely. Pink bars represent the percentage of females who remembered their dreams once a week. Grey bars represent the percentage of females who remembered their dreams few times in a week and the green bar represents those females who remembered their dreams nearly every night. Out of 15 females in category 1; 8 females (53.3%) remembered dreams once a week, 5 females (33.3%) remembered dreams few times a week and 2 females (13.3%) remembered dreams nearly every night. From 20 females in category 2; 8 females (40%) could rarely remember their dreams, 7 females (35%) remembered dreams once a week, 2 females (10%) remembered dreams few times a week and 3 females (15%) remembered dreams nearly every night. In category 3; 12 females (48%) out of 25 could rarely remember their dreams, 9 females (36%) remembered dreams once a

week and 4 females (16%) remembered dreams rarely. Post Hoc test was applied on all three categories and the significance value was found. The p value after comparing group 1 & 3 was statistically significant being 0.006 showing that the females of group 1 remembered dreams more than the females of group 3.

The p value after comparing group 1 & 2 and 2 & 3 was not statistically significant being 0.144, 0.674 respectively meaning thereby the females of these groups had almost same dream memory.

**TABLE-I: COMPARISON BETWEEN PREMENOPAUSAL AND POSTMENOPAUSAL FEMALES ON THE BASIS OF THEIR SERUM PROGESTERONE LEVELS AND SLEEP HABITS (n= 60)**

Groups	Mean Serum Progesterone level $\pm$ SEM (ng/ml)	Time to go to bed $\pm$ SEM	Number of awakenings per night $\pm$ SEM	Duration of sleep in hours $\pm$ SEM	Time of rise in morning $\pm$ SEM	Mode of awakening	
						Alarm	Without alarm
n 1 (30 Premenopausal females)	4.78 $\pm$ 1.18	10.26 $\pm$ 0.56	1.4 $\pm$ 0.10	6.66 $\pm$ 0.18	6.21 $\pm$ 0.06	22	08
n 2 (30 Postmenopausal females)	0.62 $\pm$ 0.08	9.58 $\pm$ 0.59	2.7 $\pm$ 0.11	5.93 $\pm$ 0.21	5.09 $\pm$ 0.21	00	30
p value	0.001****	0.413*	0.000****	0.011***	0.000****	0.000****	

**TABLE-II: COMPARISON BETWEEN PREMENOPAUSAL AND POSTMENOPAUSAL FEMALES ON THE BASIS OF THEIR DAYTIME SLEEPINESS (n= 60)**

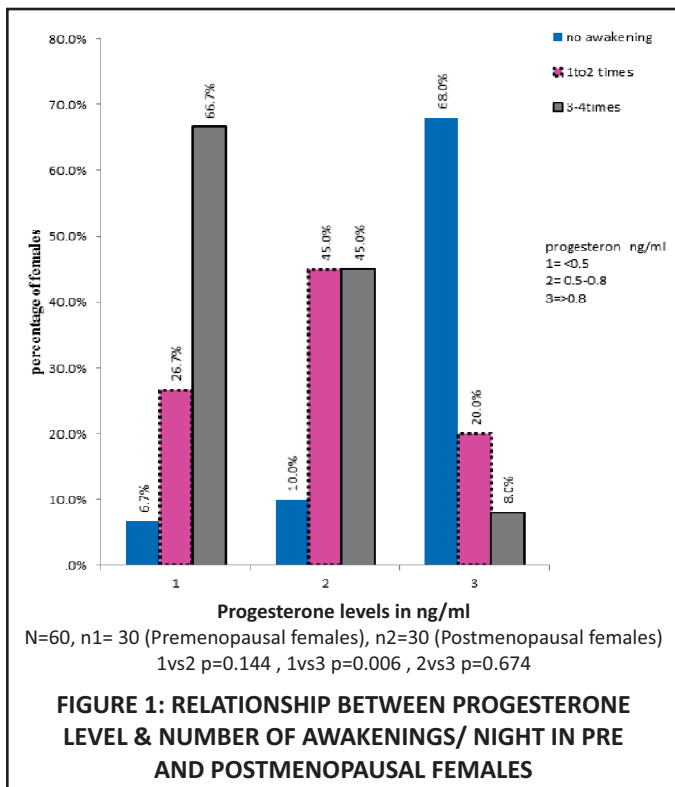
Variables	n1 (30 Premenopausal females)	n2 (30 Postmenopausal females)	p value
Feeling within 1st 30 minutes after awakening in morning	20 (66.7%)	3 (10%)	0.000***
Alert			
Somewhat drowsy but alert	10 (33.3%)	10 (33.3%)	
Drowsy	0	11(36.7%)	
Groggy	0	6 (20%)	
Number of napping per week			0.204*
Never	3 (10%)	4 (13.3%)	
< 3 times	4 (13.3%)	11 (36.7%)	
>3 times	7 (23.3%)	1 (3.3%)	
Daily	16(53.3%)	14 (46.7%)	
Feeling of tiredness in evening			0.000***
Not present	26 (86.7%)	0	
Present	4 (33.3%)	30 (100%)	

## DISCUSSION

Sleep quality is related to health, depression, fatigue and concentration. Several community based surveys about prevalence of sleep disturbances have shown that sleep disturbances increase with advancing age and especially in females especially when female approaches the age of menopause<sup>23</sup>. The average age at menopause remains approximately 51 years. With improved medical care and lifestyle choices the females' life expectancy has increased up to 80 years. Meaning thereby a female, on average, would live almost 30 years beyond her menopausal transition. In this study, the relationship between the progesterone levels with the sleep habits of females has also been evaluated and the

mean levels of serum progesterone of premenopausal and postmenopausal females were within the reference range<sup>24</sup>. During evaluation of sleep habits it was found that the wake up time in the morning of postmenopausal females was earlier than the premenopausal females. These results are similar to the study conducted by Chol Shin et al which showed that Early Morning Awakening is common in postmenopausal females<sup>24</sup>. The number of nocturnal arousals from sleep was more in postmenopausal females which is similar to a study done by Howard M. et al and Antonijevic IA et al on pre and postmenopausal females which states that poor sleep maintenance, increase in REM sleep frequency and increased number of awakenings at night are more common in postmenopausal females<sup>25,26</sup>. It was found that all the



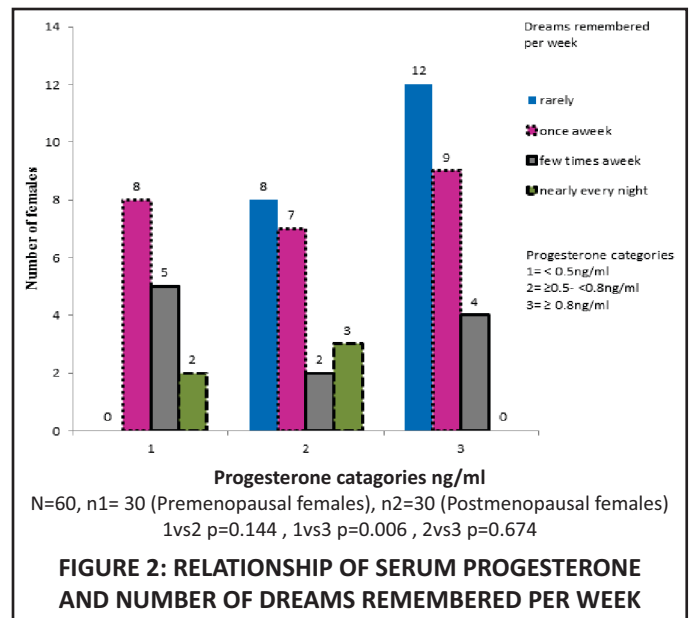


postmenopausal females awoke without using an alarm while most of the premenopausal females needed an alarm to wake up in the morning. A study conducted on elderly individuals stated that with advancing age the circadian phase is also advanced so the elderly persons tend to get up earlier in the morning. The total duration of sleep of sleep of postmenopausal females was less than the normal recommended sleep duration and was also less than that of premenopausal females. This can be explained with reference to a study conducted by Norman Wolkove et al on elderly individuals stated that with advancing age the circadian phase is also advanced so the elderly persons tend to get up earlier in the morning<sup>27</sup>.

The comparison showed that most of the postmenopausal females felt evening tiredness but very few premenopausal females felt tiredness in the evening. This can be explained on the basis of fact that postmenopausal females woke up earlier in the morning, they had less than normal sleep duration and had more frequency of arousal from sleep at night and hence they felt drowsy in the morning and tired in evening. A study conducted by Daniel et al on postmenopausal females also showed that day time sleepiness; napping and falling asleep during day time may result from poor sleep quality at night<sup>28</sup>.

The serum progesterone levels were compared with the dream memory of females in the study. It was found that the dream memory was more with lower progesterone levels. This can be explained on the basis of the fact that low progesterone levels increase the frequency of REM sleep and most of the dreams which can be recalled occur during REM sleep. This finding is also supported by a study done by Deurveilher et al which showed that progesterone replacement decreases the REM episodes in ovariectomised rats<sup>29</sup>.

In the study it was found that the lesser the serum progesterone



levels in the females; the more the number of awakenings at night, earlier the morning wakeup time and lesser the total duration of sleep in hours. According to study conducted by Baker et al shows that during the mid luteal phase there is increased SWS and decreased REM sleep and in late luteal phase there is increased frequency of microarousals at night<sup>30</sup>. A study conducted by Deurveilher et al in 2011 on postmenopausal females to see the sleep promoting effects of progesterone showed that when postmenopausal females were given progesterone replacement; their sleep quality improved with increased SWS and decreased REM episodes<sup>29</sup>. Another study done by Shechter et al on sleep habits of females showed that high progesterone levels in mid luteal phase decreased the frequency of REM sleep as compared to mid follicular phase<sup>31</sup>.

**CONCLUSIONS**

The study revealed that the serum progesterone levels affect the sleep pattern of females across the menstrual cycle and menopause. As the serum progesterone levels decline after menopause; the sleep habits of females get affected and have relatively poor sleep quality, more evening tiredness and more dream remembrance as compared to premenopausal females.

**RECOMMENDATIONS**

Progesterone and/or combined with estrogen replacement can produce positive effects in postmenopausal females with sleep disturbances by improving the sleep quality by decreasing the REMS, increasing SWS, decreasing nocturnal arousals and sleep onset latency. This can lead to a sleep pattern resembling that of younger subjects and hence improving the quality of life in postmenopausal females with sleep disturbances.

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