MAIN NEUROENDOCRINE FEATURES AND THERAPY
IN PRIMARY SLEEP TROUBLES

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MAIN NEUROENDOCRINE FEATURES AND THERAPY IN PRIMARY SLEEP TROUBLES (Abstract): Insomnia is a sleep trouble in which the patient has difficulties in falling or in staying asleep. There are patients who fall asleep easily, but wake up too early; others have troubles in falling asleep and a third category has troubles with both falling and staying asleep. Independent of the type of insomnia, the final result is a poor-quality sleep, responsible for depressive or irritable mood, loss in concentration, learning and memory capacities. Sleep is essential to emotional and physical health. Inadequate sleep over a period of time is increasing the risks for obesity, diabetes, heart disease and depression. People suffering of chronic insomnia show an increased predisposition for psychiatric problems. People who had sleep troubles reported impaired ability to fulfill tasks involving memory, learning, logical reasoning and mathematical operations. New studies show that insomnia might be a result of the decrease of gamma-aminobutyric acid (GABA), a neurochemical responsible for the decrease of activity in many brain areas. Lower brain GABA levels were also found in people with major depressive disorder and anxiety disorders. Hypnotics, such as benzodiazepines are acting increasing the activity of the GABA neurons. Exposure to stress is associated with a greater risk for insomnia, with individual differences. Stress activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Increased activity of HPA axis is stimulating the secretion of corticotropin-releasing hormone, further inducing sleep disruption. Insomnia is also associated with depression and anxiety disorders, in which the HPA axis is characteristically overactive. People who show predisposition to sleep troubles have a hyperactive sympathetic nervous system, they are usually suffering from hyperarousal and they have a more intense response to stressful events. Primary sleep troubles (insomnia) has no apparent causes, is lasting more than one month, and is affecting approximately a quarter of the adult population. Secondary insomnia is associated with chronic heart and/or lung diseases, medication which interfere with onset or duration of sleep, constant change of the sleep habits, restless leg syndrome, etc. Besides lifestyle changes and cognitive-behavioral therapy, in the treatment of insomnia are used hypnotic medicines, advised to be prescribed on short-term cures of one or two weeks. Benzodiazepines are inducing and maintaining sleep. Longer use is responsible for severe side effects – dependency and withdrawal syndrome, daytime drowsiness and dizziness, low blood pressure, memory troubles and change in the melatonin secretion during night-time period. For these reasons were created non-benzodiazepines hypnotics – zolpidem, zaleplon, which are as effective as benzodiazepines, but have fewer side effects. Nevertheless the use of these hypnotics is also restricted to 7 – 10 days. Zopiclone (Imovane) another short-acting non-benzodiazepine hypnotic
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has a different chemical structure, but a pharmacologic profile similar to that of the benzodiazepines; the treatment should be of maximum four weeks. Besides generally known concerns related to the use of hypnotics (residual sedative effects, memory impairment, rebound insomnia, abuse, dose escalation, dependency and withdrawal problems) it was signaled a risk of death associated with the use of current hypnotic medications. **Key words:** SLEEP TROUBLES, INSOMNIA, HYPNOTIC MEDICATION

**DEFINITION, OCCURRENCE, TYPES, SYMPTOMS AND RISKS OF PRIMARY SLEEP TROUBLES**

Insomnia is a sleep trouble characterized by the difficulty in falling or in staying asleep. There are patients who fall asleep easily, but wake up too soon, others have troubles in falling asleep and finally, the third group has troubles with both falling and staying asleep. Indifferent of the type of insomnia, the result is a poor-quality sleep. This situation is responsible for an inactive mind along the day and the lack of refreshness after sleep. In this view, insomnia is the most common cause of depressive or irritable mood, loss in concentration, learning and remembering. Sleep is essential to physical and emotional health. Inadequate sleep over a period of time is associated with obesity, diabetes, heart disease and depression (Stores 2007, Schroeder 2005). Emotional and mental benefits of sleep are significant. Some people with chronic insomnia show an increased predisposition for psychiatric problems. People who had sleep troubles reported impaired ability to fulfill tasks involving memory, learning, logical reasoning and mathematical operations (Estivill 2003).

In contrast with the secondary insomnia, which is related with other diseases or troubles, being the most common type, the primary insomnia appears without any coexisting cause, it lasts at least one month and is found at approximately a quarter of the adult population. Secondary insomnia is found in eight people of ten with insomnia. Some of the major causes of secondary insomnia are – heart and/or lung chronic diseases, medicines which interfere with onset or duration of sleep, substances like caffeine, tobacco and alcohol, constant change in sleep routine or a poor sleep environment, restless legs syndrome. Main symptoms associated with insomnia are poor concentration, impaired motor coordination and memory troubles, depressive or irritable mood (Silber 2005, Sateia 2009, Panossian 2009).

**NEUROENDOCRINE FEATURES OF THE PRIMARY SLEEP TROUBLES**

Many adults suffering from insomnia complain of an inability to “shut down” their mind at night. New studies show that this is a result of the decrease of gamma-aminobutyric acid (GABA). People with primary insomnia with more than six months have 30 % less GABA, a neurochemical responsible for the decrease of activity in numerous brain areas. Lower brain GABA levels have also been found in people with major depressive disorder and anxiety disorders. Primary insomnia has a lot of features in common with these conditions, being as well a critical risk factor (Winkelman 2009, Riemann 2003, Roth 2007). In this view, the GABA deficiencies found in people with mood and anxiety
disorders, might be linked to sleep disturbances. Many hypnotic medications, most effective in treating insomnia, are benzodiazepine receptor antagonists (BzRAs) which increase the activity of the GABA neurons. Besides sleep, GABA is involved in cognitive, memory and psychomotor functions.

Exposure to stressful events is usually associated with a greater risk for insomnia, with individual differences. Stress factors activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis (HPA). In insomniacs there is an increased activity of HPA axis, which by secretion of corticotropin-releasing hormone is further producing sleep disruption. Sleep loss is also activating HPA axis. Insomniacs have reduced melatonin levels at night, while corticotropin-releasing hormone was demonstrated to reduce nocturnal melatonin levels, in normal subjects (Passarella 2008).

These data suggest that HPA hyperactivity may be involved in neuroendocrine changes that lead to insomnia. Furthermore, insomnia is associated with depression and anxiety disorders, in these illnesses the HPA axis is characteristically hyper activated. People which show predisposition to sleep troubles have an overactive sympathetic system; they are more likely to suffer from hyper arousal and have a more intense response to stressful events (Benca 2005, Roth 2007).

THERAPY OF THE PRIMARY SLEEP TROUBLES

Treatment options for insomnia include lifestyle changes, cognitive-behavioral therapy and sleep or hypnotic medications. Lifestyle changes are focusing on good sleep habits: dark and quiet bedroom, with adequate temperature; avoidance of over-intake of caffeine, alcohol, tobacco or other stimulants; avoidance of medicines that disrupt sleep; stable bedtime habits – going to bed at the same hour. Cognitive-behavioral therapy includes relaxation training and biofeedback at bedtime, to reduce anxiety; positive thinking and replacing worries related to falling asleep; talking to therapists; reduction of time spend in bed while awake (Smith 2002, Morin CM 2009). Usually, sleeping pills are prescribed only for one or two weeks, helping to establish a regular sleep schedule. Sleep medication can become habit-forming, thus it is considered that sleep medication works best as a short-term treatment, combined with lifestyle and behavior changes.

Benzodiazepines are used for short-term relief from insomnia. They induce sleep and they maintain sleep. Examples such as diazepam (Valium), lorazepam (Activan) or quazepam (Doral) have troubling side effects – dependency and withdrawal syndrome, daytime drowsiness and dizziness, low blood pressure, especially in older people and memory troubles (Cotroneo 2007). They affect the melatonin secretion, during the night-time period (Garfinkel 1999). Using such hypnotics may also worsen sleep apnea and other breathing disorders (Budur 2007, Schutte-Rodin 2008).

Zopiclone (Imovane) is a short-acting hypnotic. Zopiclone is a cyclopyrrolone derivative, with a structure unrelated to other hypnotics. However, the pharmacologic profile of zopiclone is similar to that of the benzodiazepines. In sleep laboratory, studies of one to 21 days duration in man, the hypnotic reduced sleep latency, increased the sleep-duration and reduced the
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number of nocturnal awakenings. Zoplicone delayed the onset of REM sleep, but did not reduce consistently the total duration of REM periods. The course of treatment should be of maximum 4 weeks as duration. The most common adverse reaction of zoplicone is taste alteration (bitter taste). Drowsiness, dizziness, somnolence, asthenia, may be signs of intolerance or excessive doses (Dundar 2004). Non-benzodiazepines hypnotics, zolpidem and zaleplon are short-acting, being as effective as benzodiazepines. They have fewer side effects and lesser withdrawal symptoms. They are used as alternative therapy and to treat the dependency and withdrawal problems induced by benzodiazepines. However the use of these hypnotics is also restricted to 7 – 10 days. Some studies have signaled dependency and withdrawal symptoms with these medicines too. Expert opinion is strongly against long-term drug treatment because of possible residual sedative effects, memory impairment, falls, respiratory depression, rebound insomnia, abuse, dose escalation, dependency and withdrawal difficulties and an increased risk of death possibly associated with the use of current hypnotic medications (Wagner 2000, Barbera 2005, Morin A K 2007).

REFERENCES

7. Winkelman JW et al. Reduced brain GABA in primary insomnia : preliminary data from 4T proton magnetic resonance spectroscopy (1H-MRS), American Academy of Sleep Medicine, Sleep Conference Jun 2009; Abstract Suppl: 284.

**IMPULSIVITY COULD BE DECREASED BY HIGHER DOPAMINE LEVELS**

Dopamine is a neurotransmitter that plays a key role in motivations, mood, learning, cognition, behavior and attention. Higher levels of dopamine in the frontal cortex of the brain decrease impulsivity, according to a study conducted by Kayser et al. Impulsivity characterizes subjects with frontal lobe damage and behavioral disorders and is a common risk factor associated with substance abuse. To test the hypothesis that lower dopamine in the frontal cortex contributes to impulsivity by impairing corticostriatal function, researchers performed a randomized, double-blind, placebo-controlled study in which they administered the brain penetrant catechol-O-methyltransferase inhibitor tolcapone or placebo to healthy subjects performing a delay discounting task. The results of the study showed that tolcapone significantly increased choice of delayed monetary rewards and also changed corticostriatal connectivity by inducing a decrease in the coherence between ventral putamen and pregenual cingulate cortex. In conclusion, the study states that raising cortical dopamine levels attenuates impulsive choice by changing corticostrital connectivity, and intertemporal choice. *(Kayser AS, Allen DC, Navarro-Cebrian A et al. Dopamine, corticostriatal connectivity, and intertemporal choice. *J Neurosci* 2012; 32(27): 9402-9)."