# Sleep Disorders in Parkinson's Disease

**Prachaya Srivanitchapoom, M.D., Niphon Poungvarin, M.D., FRCP (London).**
*Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

## ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disease that is associated with degeneration of dopaminergic neurons in the substantianigra. Therefore, patients who are diagnosed with PD will exhibit clinical symptoms of dopaminergic depletion including motor and non-motor symptoms. Previously, physicians (please see comment on page 4) and researchers have been most interested in the aspect of motor problems. However, more recently, non-motor symptoms (NMS) have received similar recognition to motor symptoms. Some of the most common NMS are sleep disorders. The prevalence of sleep disorders ranges from 40 to 90 percent and the common sleep problems in patients with PD are insomnia, excessive daytime sleepiness, rapid eye movement, sleep behavior disorders, sleep related breathing disorders, restless leg syndrome and nocturia. This article includes the epidemiology, etiologies, common patterns and managements of sleep disorders in patients with PD.

**Keywords:** Sleep disorders in Parkinson disease, insomnia, rapid eye movement behavior disorders, restless leg syndrome, obstructive sleep apnea, nocturia

**Siriraj Med J 2013;65:88-95**
***E-journal: http://www.sirirajmedj.com***

## INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease relating to progressive degeneration of dopaminergic neurons in the substantianigra. The diagnostic criteria of PD were defined in a clinico-pathological study proposed by United Kingdom Parkinson's Disease Society (UKPDS) in 1988.[1] The consequence of degeneration of these neurons is depletion of dopamine in the central nervous system. Therefore, patients diagnosed with PD will exhibit clinical symptoms of dopaminergic depletion such as motor and non-motor symptoms (NMS). Motor symptoms in PD have been recognized in terms of four cardinal characterizing features; resting tremors, bradykinesia, rigidity and postural instability. Recently, NMS, such as autonomic dysfunctions, fatigue, pain, sleep disorders, hyposmia, abnormal behaviors and neuropsychiatric manifestations have become increasingly recognized.[2] NMS occur in up to 60 percent of patients with PD.[2,3] Some of the most common NMS are sleep disorders.[4] The significant impact of sleep disorders on patients with PD is in poor quality of life when compared with the normal population.[5,6] This article will focus on the epidemiology, possible causes of sleep disorders, scale systems to assess sleep impairment in PD, common sleep problems of patients with PD and current managements.

### Epidemiology

The prevalence of sleep disorders in patients with PD ranges from 40 to 90 percent.[4,6,7] This figure was supported by a recent study conducted by Goetz et al. The study showed a high prevalence of sleep disorders that approached to 98 percent at 10-years of follow-up.[8] According to Braak's postulation, sleep disorders can develop in any state of PD such as the pre-motor state, the motor state or the advanced state. The evidences of sleep disorders which develop in the pre-motor state have been confirmed by many studies. Abbott and colleagues demonstrated that elderly who had excessive daytime sleepiness (EDS) were at a higher risk of developing PD when compared to subjects who did not present EDS (odds ratio = 3.3, 95% CI = 1.4 to 7.0, pvalue = 0.004)[9]. Another study conducted by Claassen et al found that 4.9 percent of patients with rapid eye movement sleep behavior disorder (RBD) subsequently developed parkinsonism and/or dementia (PD, diffused Lewy body dementia (DLB), or multiple system atrophy (MSA)) and that the latency between the onset of RBD and other clinical features

*Correspondence to: Niphon Poungvarin*
*E-mail: sinpg@mahidol.ac.th, clound@hotmail.com*
*Received 4 January 2013*
*Revised 22 March 2013*
*Accepted 9 April 2013*

was at least 15 years.[10] A study of the overall prevalence of sleep disorders in Thai patients with PD has not been conducted yet.

Common sleep problems of patients with PD are insomnia, EDS, RBD, sleep related breathing disorders (SRBD), restless legs syndrome (RLS) and nocturia.[11]

## Etiologies of sleep disorders in patients with PD

Appropriation of sleep activity is usually based upon the interaction between the individuals and the environmental circumstances such as either light or dark environments and either noisy or silent environments. Despite the control of environmental factors, patients with PD also have various causes that disturb their sleep activity. The etiologies can be grouped into three categories; 1) PD related to sleep disorders, 2) specific causes of sleep disorders and 3) treatments related to sleep disorders. The possible causes of sleep disorders related to patients with PD have been summarized in Table 1.[11,12,13]

## Scale systems to assess sleep impairment in PD

Because of the high prevalence and various types of sleep disorders in PD, researchers have developed many tools for detecting these sleep problems such as sleep scales or neurophysiologic methods. Unfortunately, the neurophysiologic studies are expensive, are time consuming and require a sleep medicine subspecialist to interpret the results. Thus, the sleep scales have become more popular. The benefits of sleep scales are that they are easy to use in out patient or community-based settings, inexpensive and mostly self-assessed. However, using the scales has some limitations in determining problems. First of all, assessment by sleep scale is subjective evidence. If the patient or caregiver lacks awareness of sleep problems, the result will not be accurate. Another limitation is the patient with PD may develop multiple types of sleep disorders. Due to this reason, a physician may need many sets of scales for detecting sleep problems in one patient. Finally, if a patient develops cognitive impairment, the data gathering and data interpretation will be of diminished accuracy.

The PD Sleep Scales (PDSS)[14] is the most popular scale for screening sleep disturbances and the severity of sleep problems over the previous week including both nighttime and daytime symptoms. This scale is composed of 15 items. Each item is rated by a visual analog scale from 0 (most severe) to 10 (no disturbance) with a higher score reflecting a better sleep quality. This scale is a screening test. It has no power to diagnose the specific sleep problems such as RBD, SRBD and RLS. Another scale is the Pittsburgh Sleep Quality Index (PSQI),[15] a self-assessment scale that was proposed to assess sleep quality over the previous month. This scale is composed of 19 items. Each item is categorized into 4 sub-scores with, 0, 1, 2 or 3 points, respectively. Then each item is combined to create 7 components following the instructions of a protocol. The maximum score is 21 points with a higher point reflecting a lower sleep quality. The cut-off point indicating a poorer sleep quality is more than 5 points. Similar to the PDSS, this scale is only a screening test. The Scales for Outcome in PD (SCOPA-SLEEP)[16] was developed for evaluating daytime sleepiness and sleep quality in PD over the past month. This scale is composed of 3 sub-scales; a nighttime scale, a sleep quality scale and a daytime scale. The nighttime scale is composed of 5 items (rated from 0 to 3 points for each item). Thus, the maximum score is 15 points with a higher point reflecting greater nighttime sleep problems. The sleep quality scale is a single item referring to a global measurement of sleep quality. The daytime scale is composed of 6 items (rated from 0 to 3 points for each item). Thus, the maximum score is 18 points with a higher point reflecting greater

**TABLE 1.** The possible causes of sleep disorders in patients with PD

| |
|---|
| 1) PD related sleep disturbances |
| 1.1) Nocturnal motor symptoms |
| 1.1.1) Tremors |
| 1.1.2) Dystonia |
| 1.1.3) Dyskinesia |
| 1.1.4) Rigidity, akinesia |
| 1.1.5) Limbs jerking |
| 1.2) Nocturnal non-motor symptoms |
| 1.2.1) Autonomic dysfunction e.g. urinary incontinence |
| 1.2.2) Neuropsychiatric manifestations e.g. dementia, delusion, hallucination, depression and anxiety |
| 1.2.3) Sensory disturbances e.g. muscle cramp and pain |
| 2) Specific sleep disorders |
| 2.1) Dyssomnias e.g. insomnia, excessive daytime sleepiness (EDS) |
| 2.2) Parasomnia e.g. rapid eye movement sleep behavior disorder (RBD) |
| 2.3) Sleep related breathing disorders (SRBDs) e.g. obstructive sleep apnea (OSA) |
| 2.4) Restless leg syndrome (RLS)/Periodic limb movement during sleep |
| 2.5) Circadian rhythm disruption |
| 3) Treatments related sleep disturbances |
| 3.1) Medication e.g. levodopa, dopamine agonist, MAOB inhibitor,anticholinergics and antipsychotics |
| 3.2) Deep brain stimulation (DBS) |
| MAOB – Monoamine oxidase B, COMT – Catechol-o-methyl transferase |

daytime sleep problems. Similar to PDSS and PQSI, this scale is only a screening test and measures the severity for sleep problems in PD. The Epworth Sleepiness Scales (ESS)17is the most popular scale for detecting the daytime sleepiness symptoms in a varietyof population groups. This scale is composed of 8 items (rating from 0 to 3 points for each item). The maximum score is 24 points and the cut-off point for indicating obvious daytime sleepiness is more than 10 points. The ESS has more sensitivity and specificity to detect daytime sleepiness, but various conditions such as anxiety, depression and somatization can interfere with this test. SRBD is diagnosed by the presentation of snoring, hypopnea and apnea. Usually, the information is received from the patient's sleep partner. The tool that helps physicians (In the abstract you referred to clinicians and here you refer to physicians. It would be better to use consistent terms, so I changed the abstract to physicians.) to diagnose this condition is polysomnography by measurement of the apnea-hypopnea index (AHI). The cut-off pointof AHI for diagnosis of SRBD is more than 5 points and a patient shows desaturation[18]. RLS is diagnosed by criteria from the International RLS Study Group (IRLSSG)[19]. The criteria are composed of; 1) an urge to move the legs, 2) usually accompanied by uncomfortable and unpleasant sensations, 3) onset or aggravation during periods of inactivity, and 4) relief by movement and worsening in the evening or at night. RBD is diagnosed by history from their sleep partner of shouting, walking or kicking with definite diagnosis requiring polysomnography. The RBD screening questionnaire (RBDSQ)[20] is a promising tool for screening RBD, but validation in different populations is required. Finally, detection of nocturia is a clinical observation. The International Prostate Symptom Score (IPSS),[21,22] includes 7 items. Question number 7 is for screening the symptom of nocturia and is used for detecting nocturia and other urinary symptoms in both men and women in a variety of population groups. A higher score reflects greater urinary problems which produce a negative impact on sleep quality.[23]

## Common sleep problems of patients with PD and managements

### Insomnia

The clinical characteristics of insomnia are defined as at least one symptom of difficulty in falling asleep, difficulty to maintain sleep, early awakening, or inability to get refreshing sleep occurring despite adequate opportunities for sleep. Among the characteristics of insomnia, the category of difficult sleep maintenance, which causes greater sleep fragmentation and frequent night awakening, is the most common pattern of insomnia in patients with PD. The consequences of disruption of sleep maintenance are reduction of total sleep times and increasing daytime somnolence from circadian rhythm disruption.[11,12] The various causes of disturbance of sleep maintenance are identified as; abnormal movements associated with primary PD pathology or associated with anti-parkinsonian medication, and frequent nocturia or neuropsychiatric manifestations such as delusion, hallucination or depression. Previously, Lee and colleagues showed factors disturbing sleep maintenance overnight in patients with PD including; nocturia (79%), difficulty of turning over in bed (65%), painful muscle cramps (55%), nightmares (48%), limb or facial dystonia (34%), jerking of legs (33%), and visual hallucinations (16%).[24]

Another cause of insomnia in patients with PD is anti-parkinsonian medications such as Monoamine oxidase B (MAOB) inhibitors, particular in selegiline because a metabolite of selegiline is a derivative of amphetamine. Therefore, patients with PD prescribed selegiline in the evening or before bedtime may develop insomnia. Insomnia is associated with the duration of PD, the severity of motor symptoms, complications of dopaminergic treatments and depression.[25]

Managements include demonstrating and correcting the factors that disturb the sleep-wake cycle such as inappropriate environment, abnormal movements during nighttime (dyskinesia, akinesia, tremor, RLS), and neuropsychiatric symptoms (hallucination, delirium, depression, anxiety). If those factors are corrected and patients still have sleeping difficulties, the physician can consider prescribing medications. Zolpidem, a non-benzodiazepine, that has been approved by United States Food and Drug Administration (U.S. FDA) for treating insomnia should be considered.[26] Other medications such as eszopiclone,[27] melatonin[28] and low dose quetiapine[29] may have some potential for improving insomnia.

Excessive Daytime Sleepiness (EDS)

Another entity of diurnal alterations of sleep pattern is EDS. EDS is defined by the Epworth Sleepiness Scale (ESS) as being more than 10 points or a mean sleep latency less than 5 minutes on the Multiple Sleep Latency Test.[30,31] Previous epidemiologic studies showed the prevalence of EDS in patients with PD ranged from 15 to 50 percent.[7,13,31] EDS creates negative impacts to quality of life such as automobile accidents.[32,33] The manifestations of EDS are divided into two types.[33] First, patients know that they feel sleepy in the daytime and they try to resist it, but they cannot avoid falling asleep. Second, the sudden onset of sleep was described by Frucht et al., who coined the term "sleep attack". In sleep attack, patients do not have self-awareness which is similar to narcolepsy. The differential symptom between PD and classic narcolepsy is that patients with PD have a lack of clinical cataplexy.[34] The role of low orexin levels in the cerebrospinal fluid (CSF) of patients with PD is controversial for differentiating between narcolepsy and sleep attack.[35,36] Sleep attack was initially described in two patients with PD who took dopamine agonists, one took pramipexole and the other took ropinirole. Both patients developed sudden onset of sleep while driving.[32] Factors which are associated with EDS are; longer duration of PD, high disease severity and male gender.[13,31,37] The predisposing factors of EDS are dopaminergic medications in particular dopamine agonists, dementia, depression, hallucination, circadian rhythm disruption, disease severity, disease duration and obstructive sleep apnea (OSA).[37]

Similar to insomnia, physicians should search and

correct factors that disrupt the sleep-wake cycle. Physicians should stop the medications that cause nighttime awakening such as selegiline. All anti-parkinsonian medications can cause EDS in particular dopamine agonists. Reducing dosage or discontinuation of dopamine agonists should be considered in patients with sleep attack. If the patients cannot tolerate to reduce their anti-parkinsonian medications because of worsening motor symptoms, administration of psycho-stimulants such as modafinil,[38,39,40] armodafinil,[41,42] sodium oxybate[43] and tiprolisant[44] should be considered.

## Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD)

RBD is categorized in the subgroup of parasomnias. Characteristic of RBD are defined as loss of muscle atonia during REM sleep period, proven by electromyography, which results in dream-enacting behavior associated with nightmares or vivid dream. In REM sleep periods, patients may shout, kick, or jump out of their bed which often leads to injury of the individual or their bed partner. The brain areas that may play a role in the pathophysiology of RBD were described to be the locus coeruleus, the pedunculopontine nuclei, the cholinergic nuclei, the laterodorsal tegmental nuclei and the limbic area.[2,45] According to the data from Scheck et al, many recent studies have shown a relationship between RBD and the risk of developing PD and other synucleinopathies associated neurodegenerative disorders such as MSA and DLB.[46] One study reported a cumulative risk of developing neurodegenerative disorders in patients with RBD as 17.7, 40.6 and 52.4 percent at 5,10 and 12-years of follow-up, respectively.[47] RBD can occur in all states of PD. The latency between RBD and the onset of motor symptoms ranges from 15 to 50 years (mean = 28.4 years).[10] Idiopathic RBD patients present with some non-motor manifestations that can found in PD, and other synucleinopathies associated neurodegenerative disorders, such as olfactory deficits,[48,49] color vision impairment,[48] cognitive impairment on neuropsychological testing,[50] slowing of electroencephalography,[51] abnormalities of cardiogenic autonomic nervous systems,[52,53] and reduced cardiac 123I-MIBG scintigraphy.[54] These finding suggest that idiopathic RBD may share some pathophysiology with PD. Almost all patients with PD who develop clinical signs of RBD are of the non-tremor phenotype, exhibiting; frequent falling, poor response to dopaminergic medications, orthostatic hypotension and impaired color vision. On the other hand, disease severity and motor complications did not differ between patients with PD together with RBD and those without RBD.[55,56] Some medications potentially induce RBD such as antidepressants; for example,selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors (SNRI), beta-blockers and barbiturates.[57]

Medications that can relieve symptoms of RBD in idiopathic RBD and RBD associated with PD are similar. Clonazepam, a long acting benzodiazepine, is the most effective medication for controlling symptoms of RBD.[58] Other medications such as melatonin,[59,60] pramipexole,[61,62] zopiclone, levodopa, sodium oxybate[63] and donepezil[64] have been reported for efficacy in controlling symptoms of RBD.

## Sleep Related Breathing Disorders (SRBD)

SRBD or sleep apnea syndromes have been observed in patients with PD. Previous studies have shown the prevalence of SRBD ranges from 20 to 66 percent in patients with PD.[65,66] The most common clinical syndrome observed in PD is OSA. OSA is defined as; heavy snoring, an apnea-hypopnea index of more than 5 and oxygen desaturation. The severity of OSA in PD usually presents in a mild to moderate degree when compared with primary OSA.[18] A recent study has shown that the rate of OSA in patients with PD does not significantly differ from the general population.[67] In contrast, one study showed the rate of sleep apnea was less observed in PD than in an in-hospital control group who exhibited daytime sleepiness that was caused by non-apneic mechanisms (27 percent versus 40 percent).[68] In summary, the relationship between SRBD and PD is inconclusive. Two possibilities that could explain clinical symptoms of upper airway obstruction in patients with PD have been proposed; 1) dysfunction of upper airway muscles due to akinesia or dyskinesia[69] and 2) vocal cord abductor dysfunction that can cause sudden death during the nighttime.[70]

The important issues of OSA are increasing cardiovascular events and upper airway obstruction at nighttime. Both conditions are life threatening. Therefore, physicians must ask the patient's partner for the frequency and the duration of apnea intervals and the frequency of nighttime awakening. If the patient's partner notices this condition, the patients must be scheduled to have polysomnography performed. Additionally, the physician should make a decision to treat the patient with a continuous positive airway pressure ventilation method.

## Restless Leg Syndrome (RLS)

RLS is a clinical diagnosis that is diagnosed by criteria from the IRLSSG (mentioned earlier).[19] Therefore, RLS can disturb the sleep-wake cycle and produce insomnia. Previous epidemiologic studies have reported the prevalence of RLS in PD ranges from 0 to 49 percent.[19,71] A recent study that was conducted by Bhalsing and colleagues from India showed the prevalence of RLS in neurodegenerative diseases compared with healthy controls. According to the results of this study, the prevalence of RLS in the neurodegenerative disease group was higher than in the control group (9.6 vs. 2.9 percent; p=0.009) and the prevalence of RLS in PD (11.9 percent) was higher than in MSA, PSP and DLB.[72] The explanations for this variety of prevalences of RLS in PD are: dopaminergic agents diminishing motor symptoms, which include RLS symptom and some patients recognizing RLS symptoms as part of PD. At present, the pathogenesis of RLS is still unknown and the relationship between the pathogenesis and neuropathology of RLS and PD is inconclusive. Most researchers suggest that RLS might share the same pathogenesis as PD. The supportive evidence is clinical response to dopaminergic agents such as dopamine agonists similar

to PD. However, autopsy study showed a low level of iron deposit in the substantia nigra[73] in contrast with PD, which showed a high level of iron deposit in the substantia nigra.[74] Another possible pathogenesis is iron or ferritin deficiency. Low serum ferritin level, less than 50 ng/mL was observed in RLS. Furthermore, some studies have shown that low iron and ferritin levels in the CSF were also detected in patients with RLS.[75,76] The interaction between iron depletion and dopaminergic dysfunction is unclear. However, a previous study in an animal model conducted by Zhao et al., showed that the synergistic effect of iron deficiency and dopamine depletion could significantly worsen the symptoms of RLS compared with only the dopamine depletion group. In addition, this study also found that iron deficiency and dopaminergic depletion produced a high degree of reduction of the binding capacity of dopamine receptor subtype 2 (D2)[77]. Symptoms of RLS are aggravated by caffeine, alcohol, and several medications such as antihistamines, dopamine antagonists, tricyclic antidepressants and SSRI[78]. Another possible pathogenesis of RLS is genetic transmission. A previous epidemiologic study showed that the patients diagnosed with idiopathic RLS had a positive family history of idiopathic RLS at a rate of approximately 63 to 90 percent. The mode of inheritance is usually autosomal dominant.[79] Mappings of the RLS locus on the chromosome were varied depending on the ethnic group. For example, the RLS locus was located on the long arm of chromosome 14 in Italian populations,[78] the short arm of chromosome 20 in Dutch populations[81] and the long arm of chromosome 13 in Turkish populations.[82] However, the gene most reported in various populations was BTBD9 on the short arm of chromosome 6.[83]

Treatment response is individualized. It depends upon the severity of symptoms. Various medications can relieve symptoms. The first line pharmacologic treatment is dopamine agonists in particular pramipexole and ropinirole.[84,85] Both agents have been approved by the U.S. FDA for moderate to severe RLS. Another medication is levodopa. A levodopa study, involving 28 patients, showed improvement of sleep quality, increasing sleep time, and reduction of symptom of RLS.[86] In the case of non-responsiveness to dopaminergic agents, if a low serum ferritin level of less than 50 ng/mL is detected, the patients should be treated by oral ferrous sulfate. The second-line medications such as opioids[87] (methadone, oxycodone and codeine), clonazepam,[88] gabapentin[89] and pregabalin[90] should be considered in patients who do not respond to first line agents.

### Nocturia

The lower urinary tract symptoms in PD such as nocturia, urgency, frequency and urge incontinence are not uncommon. A recent multicenter study, the PRIAMO study, showed that the overall prevalence of lower urinary tract symptoms in any stage of PD was approximately 57 percent and nocturia showed a high prevalence in this group (35 percent).[91] This result is concordant with a previous study that was conducted by Campos-Sousa et al. The study reported a high prevalence of nocturia in patients with PD (greater than 60 percent).[92] The possible mechanisms of nocturia in patients with PD are divided in to 2 possibilities; 1) lower urinary tract dysfunction associated with the disease process and 2) pharmacological effects of anti-parkinsonian medications. The most possible explanation of the symptom of nocturia in PD is due to the process of detrusor overactivity. A previous study in patients with PD showed an involuntary rise in detrusor pressure in the period of filling of the bladder.[93] The explanation of detrusor overactivity is disinhibition of dopaminergic action via dopaminergic subtype 1 (D1) receptors. Normally, the micturition reflex is inhibited by the basal ganglia due to the stimulation of D1 receptors. In PD, the dopaminergic circulation in the basal ganglia circuit is reduced due to the neuronal degeneration. Because of dopaminergic depletion, the activation of D1 receptors is reduced. Therefore, the inhibition of the micturition reflex by the basal ganglia is decreased causing detrusor overactivity[94]. Another possible mechanism that causes nocturia is the pharmacological effects of anti-parkinsonian medications. The effect of levodopa on urinary dysfunction has been studied and the results were inconclusive. One study conducted by Brusa et al., showed levodopa aggravated the symptoms of detrusor overactivity in the early stage of PD.[95] The other study, conducted by Winge et al., showed levodopa increased bladder capacity in patients with PD who had more troublesome bladder symptoms than at the off treatment stage.[96] More evidence that supports the inhibition of the micturition reflex via the action of the D1 receptors comes from the studies of dopamine agonists that produce a high affinity to D1 receptors. Apomorphine[97] and pergolide[98] showed improvement of detrusor overactivity in PD. The negative impact of nocturia to sleep quality in patients with PD has recently been reported.[99] The study used an objective sleep measurement by in-laboratory 48 hours polysomnography evaluation. The result showed high bother to urinary dysfunction, defined by the global bother question on the International Prostate Symptom Score (IPSS),[21,22] whose subjects had a significantly poor sleep efficiency and total sleep time.

The medication of choice for treatment detrusor overactivity and also nocturia is anticholinergic agents. The efficacy of anticholinergic agents for reducing the symptoms of detrusor overactivity has been reported from other conditions than PD. The agents such as oxybutynin[100], tolterodine XL[101] and trospium chloride[102] were studied for reducing the symptoms of detrusor overactivity from any causes. The important adverse effect of anticholinergic agents is cognitive. Therefore, the physician should be aware of these conditions when prescribing the anticholinergic agents especially in the agents that are designed to act on the central nervous system such as benzhexol.[103] Another adverse effect is urinary retention. The physician should perform the measurement of residual urine volume if the patients complain difficulty to void and empty their bladder.

## CONCLUSION

Recently, NMS in patients with PD have been recognized. Some of the most common NMS are sleep

disorders that impair the quality of life in PD. This article has reviewed the common patterns of sleep disorders that can occur in PD. Recently, sleep disturbances have been extensively studied in term of mechanism of diseases, impact on quality of life and treatment modalities. Moreover, sleep disorders do not only occur in PD, but also occur in other neurodegenerative diseases such as DLB, MSA and Alzheimer's disease. Areas of uncertainty in sleep disorders in other neurodegenerative diseases are still fascinating. Therefore, the field of sleep medicine must be extensively explored to solve many mysterious questions for the benefit of the neurodegenerative patients.

## REFERENCES


1. Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry. 1988 Jun;51(6):745-52.
2. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol. 2009 May;8(5):464-74.
3. Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, et al. International multicenter pilot study of the first comprehensive self-completed non-motor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord. 2006 Jul;21(7):916-23.
4. Kumar S, Bhatia M, Behari M. Sleep disorders in Parkinson's disease. Mov Disord. 2002 Jul;17(4):775-81.
5. Havlikova E, van Dijk JP, Nagyova I,Rosenberger J, Middel B, Dubayova T, et al. The impact of sleep and mood disorders on quality of life in Parkinson's disease patients. J Neurol 2011 Dec;258(12):2222-9.
6. Barone P, Antonini A, Colosimo C,Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: a multicenter assessment of non-motor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009 Aug 15;24(11):1641-9.
7. Tandberg E, Larsen JP, Karlsen K. Community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord. 1998 Nov;13(6):895-9.
8. Goetz CG, Ouyang B, Negron A, Stebbins GT. Hallucination and sleep disorders in PD: ten-year prospective longitudinal study. Neurology. 2010 Nov 16;75(20):1773-9.
9. Abbott RD, Ross GW, White LR, Tannaer CM, Masaki KH, Nelson JS, et al. Excessive daytime sleepiness and subsequent development of Parkinson's disease. Neurology. 2005 Nov 8;65(9):1442-6.
10. Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF.REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. Neurology. 2010 Aug 10;75(6):494-9.
11. Stacy M. Sleep disorders in Parkinson's disease: epidemiology and management. Drugs Aging. 2002 Oct;19(10):733-9.
12. Schulte EC, Winkelmann J. When Parkinson's disease patients go to sleep: specific sleep disturbances related to Parkinson's disease. J Neurol. 2011 May;258(Suppl 2):S328-35.
13. Susuki K, Miyamoto M, Miyamoto T, Iwanami M, Hirata K. Sleep disturbances associated with Parkinson's disease. Parkinsons Dis. 2011 Aug 17: doi:10.4061/2011/219056.Epub
14. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2002 Dec;73(6):629-635.
15. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193-213.
16. Marinus J, Visser M, van Hilten JJ, Lammers GJ, Stiggelbout AM. Assessment of sleep and sleepiness in Parkinson disease. Sleep. 2003 Dec 15;26 (8):1049-54.
17. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540-5.
18. Diederich NJ, Vaillant M, Leischen M, Mancuso G, Golinval S, Nati R. Sleep apnea syndrome in Parkinson's disease. A case-control study in 49 patients. Mov Disord. 2005 Nov;20(11):1413-8.
19. Allen RP, Picchietti D, Hening WA, et al. on behalf of the Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health and the International Restless Legs Syndrome Study Group Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. Sleep Med. 2003 Mar;4(2):101-19.
20. Stiasny-Kolster K, Mayer G, SchäferS, Möller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire-a new diagnostic instrument. Mov Disord. 2007 Dec 15;22(16):2386-93.
21. Barry MJ, Fowler FJ Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Associationsymptom index for benign prostatic hyperplasia. The MeasurementCommittee of the American Urological Association. J Urol. 1992 Nov;148(5):1549-57.
22. O'Leary MP. Validity of the ''Bother Score'' in the evaluation and treatment of symptomatic benign prostatic hyperplasia. Rev Urol 2005;7(1):1-10.
23. Vaughan CP, Juncos JL, Trotti LM, Johnson TM 2nd, Bliwise DL. Nocturia and overnight polysomnography in Parkinson's disease. Neurourol Urodyn. 2013 Jan 28.[Epub ahead of print]
24. Lees AJ, Blackburn NA, Campbell VL. The nighttime problems of Parkinson's disease. Clin Neuropharmacol. 1988 Dec;11(6):512-9.
25. Suzuki K, Okuma Y, Hattori N, Kamei S, Yoshii F, Utsumi H, et al. Characteristics of sleep disturbances in Japanese patients with Parkinson's disease. A study using Parkinson's disease sleep scale. Mov Disord. 2007 Jun 15;22(9):1245-51.
26. Budur K, Rodriguez C, Foldvary-Schaefer N. Advances in treating insomnia. Cleve Clin J Med. 2007 Apr;74(4):251-66.
27. Menza M, Dobkin RD, Marin H, Gara M, Bienfait K, Dicke A, et al. Treatment of insomnia in Parkinson's disease: a controlled trial of eszopi clone and placebo. Mov Disord. 2010 Aug 15;25(11):1708-14.
28. Medeiros CA, Carvalhedo de bruin PF, Lopez LA, Magalhães MC, de Lourdes Seabra M, de Bruin VM. Effect of exogenous melatonin on sleep and motor dysfunction in Parkinson's disease. A randomized, double blind, placebo-controlled study. J Neurol. 2007 Apr;254(4):459-64.
29. Juri C, Chana P, Tapia J, Kunstmann C, Parrao T. Quetiapine for insomnia in Parkinson disease: results from an open-label trial. Clin Neuropharmacol. 2005 Jun-Aug;28(4):185-7.
30. Poryazova R, Benninger D, Waldvogel D, Bassetti CL. Excessive daytime sleepiness in Parkinson's disease: characteristics and determinants. Eur Neurol. 2010 Mar;63(3):129-35.
31. Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J. Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology. 2001 Oct 23;57(8):1392-6.
32. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology. 1999 Jun 10;52(9):1908-10.
33. Iranzo A. Sleep-wake changes in the premotor stage of Parkinson's disease. J Neurol Sci. 2011 Nov 15;310(1-2):283-5.
34. Arnulf I, Leu SS, Oudiette D. Abnormal sleep and sleepiness in Parkinson's disease. Curr Opin Neurol. 2008 Aug;21(4):472-7.
35. Overeem S, Scammell TE, Lammers GJ. Hypocretin/orexin and sleep: implications for the pathophysiologyand diagnosis of narcolepsy. Curr Opin Neurol. 2002 Dec;15(6):739-45.
36. Yasui K, Inoue Y, Kanbayashi T, Nomura T, Kusumi M, Nakashima K. CSF orexin levels of Parkinson's disease, dementia with Lewy bodies, progressive supranuclear palsy and corticobasal degeneration. J Neurol Sci. 2006 Dec 1;250(1-2):120-3.
37. Tan EK, Lum SY, Fook-Chong SMC, Teoh ML, Yih Y, Tan L. Evaluation of somnolence in Parkinson's disease: comparison with age and sex-mat ched controls. Neurology. 2002 Feb 12;58(3):465-8.
38. Hogl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. Sleep. 2002 Dec;25(8):905-9.
39. Ondo WG, Fayle R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. J Neurol Neurosurg Psychiatry. 2005 Dec;76(12):1636-9.
40. Lokk J. Daytime sleepiness in elderly Parkinson's disease patients and treatment with the psychostimulant modafinil: a preliminary study. Neuropsychiatry Dis Treat. 2010 Apr 7;6:93-7.
41. Harsh JR, Hayduk R, Rosenberg R, Wesnes KA, Walsh JK, Arora S, et al. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. Curr Med Res Opin. 2006 Apr;22 (4):761-74.
42. Czeisler CA, Walsh JK, Wesnes KA, Arora S, Roth T. Armodafinil for treatment of excessive sleepiness associated with shift work disorders a randomized controlled study. Mayo Clin Proc. 2009 Nov;84(11):958-72.
43. Ondo WG, Perkins T, Swick T, Hull KL Jr, Jimenez JE, Garris TS, et al. Sodium oxybate for excessive daytime sleepiness in Parkinson disease: an open-label polysomnographic study. Arch Neurol. 2008 Oct;65(10): 1337-40.

44. Arnulf I, Leu SS. Sleepiness in Parkinson's disease. Parkinsonism Relat Disord. 2009 Dec;15(Suppl 3):S101-4.
45. Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behavior disorder and relevanceto neurodegenerative disease. Brain. 2007 Nov;130(pt 11):2770-88.
46. Iranzo A, Santamaria L, Tolosa E. The clinical and pathophysiological relevance ofREM sleep behavior disorder in neurodegenerative diseases. Sleep Med Rev.2009 Dec;13(6):385-401.
47. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir JY. Quantifying the risk of neurodegenerativedisease in idiopathic REM sleep behavior disorder. Neurology. 2009 Apr 14;72(15):1296-300.
48. Miyamoto T, Miyamoto M, Iwanami M, Hirata K. Olfactory dysfunction in Japanesepatients with idiopathic REM sleep behavior disorder: comparison of data usingthe University of Pennsylvania smell identification test and odor stick identificationtest for Japanese. MovDisord. 2010 Jul 30;25(10):1524-6.
49. Postuma RB, Gagnon JF, Vendette M, Desjardins C, Montplaisir JY. Olfaction and color vision identify impending neurodegeneration in rapid eye movement sleep behavior disorder. Ann Neurol. 2011 May;69(5):811-8.
50. Ferini-Strambi L, Di Gioia MR, Castronovo V, Oldani A, Zucconi M, Cappa SF. Neuropsychological assessment in idiopathic REM sleep behavior disorder. Neurology. 2004 Jan 13;62(1):41-5.
51. Massicotte-Marquez J, Carrier J, Décary A, Mathieu A, Vandette M, Petit D, et al. Slow-wave sleep and delta powerin rapid eye movement sleep behavior disorder. Ann Neurol. 2005 Feb;57(2):277-82.
52. Postuma RB, Lanfranchi PA, Blais H, Gagnon JF, Montplaisir JY. Cardiac autonomic dysfunction in idiopathic REM sleep behavior. Mov Disord. 2010 Oct 30;25(14):2304-10.
53. Sideworf A, Jennings D. Cardiac denervation in rapid eye movement disorder and Parkinson disease: getting to the heart matter. Mov Disord. 2010 Oct 30;25(14):2269-71.
54. Miyamoto T, Miyamoto M, Inoue Y, Usui Y, Suzuki K, Hirata K. Reduced cardiac 123I-MIBG scintigraphy in idiopathic REM sleep behavior disorder. Neurology. 2006 Dec 26;67(12):2236-8.
55. Postuma RB, Gagnon JF, Vendette M, Charland K, Montplaisir JY. REM sleep behaviour disorder in Parkinson'd disease is associated with specific motor features. J Neurol Neurosurg Psychiatry. 2008 Oct;79(10):1117–21.
56. Postuma RB, Gagnon JF, Vendette M, Charland K, Montplaisir JY. Manifestations of Parkinson disease differ in association with REM sleep behavior disorder. Mov Disord. 2008 Sep 15;23(12):1665-72.
57. Schenck CH, Mahowald MW, Kim SW, O'Connor KA, Hurwitz TD. Prominent eye movements during NREM sleep and REM sleep behavior disorder associated with fluoxetine treatment of depression and obsessive-compulsive disorder. Sleep. 1992 Jun;15(3):226-35.
58. Aurora RN, Zak RS, Maganti RK, Auerbach SH, Casey KR, Chowdhuri S, et al. Best practice guide for the treatment of REM sleep behavior disorder (RBD). J Clin Sleep Med. 2010 Feb 15;6(1):85-95.
59. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med. 2003 Jun;4(4):281-4.
60. Takeuchi N, Uchimaru N, Hashizume Y, Mukai M, Etoh Y, Yamamoto K, et al. Melatonin therapy for REM sleep behavior disorder. Psychiatry Clin Neurosci. 2001 Jun;55(3):267-9.
61. Fantini ML, Gagnon JF, Filipini D, Montplaisir JY. The effects of pramipexole in REM sleep behavior disorder. Neurology. 2003 Nov 25;61(10): 1418-20.
62. Schmidt MH, Koshal VB, Schmidt HS. Use of pramipexole in REM sleep behavior disorder: results from a case series. Sleep Med. 2006 Aug;7(5): 418-23.
63. Anderson KN, Shneerson JM. Drug treatment of REM sleep behavior disorder: the use of drug therapies other than clonazepam. J Clin Sleep Med. 2009 Jun 15;5(3):235-9.
64. Ringman JM, Simmons JH. Treatment of REM sleep behavior disorder with donepezil: a report of three cases. Neurology. 2000 Sep 26;55(6):870-1.
65. Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML. Parkinson's disease and sleepiness: an integral part of PD. Neurology. 2002 Apr 9;58(7):1019-24.
66. Maria B, Sophia S, Michalis M, Charalampos L, Andreas P, John ME, et al. Sleep breathing disorders in patients with idiopathic Parkinson's disease. Respir Med. 2003 Oct;97(10):1151-7.
67. Trotti LM, Bliwise DL. No increased risk of obstructive sleep apnea in Parkinson's disease. MovDisord. 2010 Oct 15;25(13):2246-9.
68. Cochen De Cock V, Abouda M, Leu S, Oudiette D, Roze E, Vidailhet M, et al. Is obstructive sleep apnea a problem in Parkinson's disease? Sleep Med. 2010 Mar;11(3):247-52.
69. Vincken WG, Gauthier SG, Dollfuss RE, Hanson RE, Darauay CM, Cosio MG. Involvement of upper airway muscles in extrapyramidal disorders. A cause of airflow limitation. N Eng J Med. 1984 Aug 16;311(7):438-42.
70. Isozaki E, Shimizu T, Takamoto K, Horiguchi S, Hayashida T, Oda M, et al. Vocal cord abductor paralysis (VCAP) in Parkinson's disease: difference from VCAP in multiple system atrophy. J Neurol Sci. 1995 Jun; 130(2):197-202.
71. Verbaan D, van Rooden SM, van Hilten JJ, Trenkwalder C, Walters AS, Montplaisir JY, et al. Prevalence and clinical profile of restless legs syndrome in Parkinson's disease. MovDisord. 2010 Oct 15;25(13):2142-7.
72. Bhalsing K, Suresh K, Muthane UB, Pal PK. Prevalence and profile of restless legs syndrome in Parkinson's disease and other neurodegenerative disorders: a case-control study. Parkinsonism Relat Disord. 2013 Jan 18. [Epub ahead of print]
73. Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Ondo WG, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology. 2003 Aug 12;61(3):304-9.
74. Morris CM, Edwardson JA. Iron histochemistry of the substantianigra in Parkinson's disease. Neurodegeneration. 1994 Dec;3(4):277-82.
75. Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology. 2000 Apr 25;54(8):1698-700.
76. Mizuno S, Mihara T, Miyaoka T, Inagaki T, Horiguchi J. CSF iron, ferritin and transferrin levels in restless legs syndrome. J Sleep Res. 2005 Mar; 14(1):43-7.
77. Zhao H, Zhu W, Pan T, Xie W, Zhang A, Ondo WG, Le W. Spinal cord dopamine receptor expression and function in mice with 6-OHDA lesion of the A11 nucleus and dietary iron deprivation. J Neurosci Res. 2007 Apr;85(5):1065-76.
78. Ekbom K, Ulfberg J. Restless legs syndrome. J Int Med. 2009 Nov;266 (5):419-31.
79. Hening W, Allen R, Earley C, Kushida C, Picchietti D, Silber M. The treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Review. Sleep. 1999 Nov 1;22 (7):970-99.
80. Bonati MT, Ferini-Strambi L, Aridon P, Oldani A, Zucconi M, Casari G. Autosomal dominant restless legs syndrome maps on chromosome 14q. Brain. 2003 Jun;126(Pt 6):1485-92.
81. Sas AM, Di Fonzo A, Bakker SL, Simons EJ, Oostra BA, Maat-Kievit AJ. Autosomal dominant restless legs syndrome maps to chromosome 20p13 (RLS-5) in a Dutch kindred. Mov Disord. 2010Aug 15;25(11):1715-22.
82. Balaban H, Bayrakli F, Kartal U, Pinarbasi E, Topaktas S, Kars HZ. A novel locus for restless legs syndrome on chromosome 13q. Eur Neurol. 2012;68(2):111-6.
83. Trenkwalder C, Högl B, Winkelmann J. Recent advances in the diagnosis, genetics and treatment of restless legs syndrome. J Neurol. 2009 Apr;256 (4):539-53.
84. Hansen RA, Song L, Moore CG, Gilsenan AW, Kim MM, Calloway MO, et al. Effect of ropinirole on sleep outcomes in patients with restless legs syndrome: meta-analysis of pooled individual patient data from randomized controlled trials. Pharmacotherapy. 2009 Mar;29(3):255-62.
85. Oertel WH, Stiasny-Kolster K, Bergtholdt B, Hallström Y, Albo J, Leissner L, et al. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). Mov Disord. 2007 Jan 15;22(2):213-9.
86. Wetter TC, Trenkwalder C, Stiasny-Kolster K, Pollmächer T, Kazenwadel J, Kohnen R, et al. Treatment of idiopathic and uremic restless legs syndrome with L-dopa-a double-blind cross-over study. Wien Med Wochenschr. 1995;145(17-18):525-7.
87. Walters AS, Winkelmann J, Trenkwalder C, Fry JM, Kataria V, Wagner M, et al. Long-term follow-up on restless legs syndrome patients treated with opioids. Mov Disord. 2001 Nov;16(6):1105-9.
88. Saletu M, Anderer P, Saletu-Zyhlarz G, Prause W, Semler B, Zoghlami A, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. Eur Neuropsychopharmacol. 2001 Apr;11(2):153-61.
89. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, crossover study. Neurology. 2002 Nov 26;59(10):1573-9.
90. Garcia-Borreguero D, Larrosa O, Williams AM, Albares J, Pascual M, Palacios JC, et al. Treatment of restless legs syndrome with pregabalin: a double-blind, placebo controlled study. Neurology. 2010 Jun 8;74(23): 1897-904.
91. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009 Aug 15;24(11):1641-9.
92. Campos-Sousa RN, Quagliato E, da Silva BB, de Carvalho RM Jr, Ribeiro SC, de Carvalho DF. Urinary symptoms in Parkinson's disease: prevalence and associated factors. Arq Neuropsiquiatr. 2003 Jun;61(2B):359-63.
93. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The

standardization of terminology of lower urinary tract function: report from the standardization sub-committee of the international continencesociety. Neurourol Urodyn. 2002;21(2):167-78.
94. Blackett H, Walker R, Wood B. Urinary dysfunction in Parkinson's disease: a review. Parkinsonism Relat Disord. 2009 Feb;15(2):81-7.
95. Brusa L, Petta F, Pisani A, Miano R, Stanzione P, Moschella V, et al. Central acute D2 stimulation worsens bladder function in patients withmild Parkinson's disease. J Urol. 2006 Jan;175(1):202-7.
96. Winge K, Werdelin L, Nielson K, Stimpel H. Effects of dopaminergictreatment on bladder function in Parkinson's disease. Neurourol Urodyn. 2004; 23(7):689-96.
97. Aranda B, Cramer P. Effect of apomorphine and L-dopa on the parkinsonian bladder. Neurourol Urodyn 1993;12(3):203-9.
98. Kuno S, Mizuta E, Yamasaki S, Araki I. Effects of pergolide on nocturiain Parkinson's disease: three female cases selected from over 400 patients. Parkinsonism RelatDisord. 2004 Mar;10(3):181-7.
99. Vaughan CP, Juncos JL, Trotti LM, Johnson TM 2nd, Bliwise DL. Nocturia and overnight polysomnography in Parkinson's disease. Neurourol Urodyn. 2013 Jan 28.[Epub ahead of print]
100. Bennett N, O'Leary M, Patel A, Xavier M, Erickson J, Chancellor M. Can higher doses of oxybutynin improve efficacy in neurogenic bladder? J Urol. 2004 Feb;171(2 Pt 1):749-51.
101. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the antimuscarinic clinical effectiveness trial (ACET). Curr Med Res Opin 2002;18(4):177-84.
102. Halaska M, Ralph G, Wiedmann A, Primus G, Ballering-Bruhl B, Hofner K, et al. Controlled, double-blind, multicentre clinical trial to investigate the long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. World J Urol. 2003 May;20(6):392-9.
103. Cooper J, Sagar H, Doherty S, Jordan N, Tidswell P, Sullivan E. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor functions in Parkinson's disease. Brain. 1992 Dec;115(Pt 6):1701-25.