PAIN IN PARKINSON'S DISEASE PATIENTS

Maria-Lucia Muntean, Lacramioara Perju Dumbrava
Neuroscience Department, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania

ABSTRACT

Parkinson's disease is characterized by motor features, which represent diagnostic criteria and non-motor symptoms that have greater significance when assessed by quality-of-life measures. Pain is a part of the large spectrum of non-motor symptoms. It can occur in any stage of the disease, even in the premotor-phase. Its prevalence varies between 38% and 85%, depending on the study design and inclusion criteria. Pain in PD can be classified using different criteria: its relation to PD or depending on the aggravating factors. The pathology of pain in PD in not completely clarified, but the basal ganglia seem to play an important role in the processing of pain signals. One can assess pain by measuring the pain threshold or by using scales. Treating pain in PD patients can be difficult and it implies a good management of antiparkinsonian medication, NSAIDs, antidepressants, antiepileptic drugs and physical therapy.

Key words: Parkinson's disease, non-motor symptoms, pain

INTRODUCTION

James Parkinson accurately described the motor problems of patients with 'shaking palsy', but also noted several non-motor features (NMS).(1) The motor disorder of Parkinson's disease has been extensively researched resulting in improved diagnostic accuracy and development of robust rating scales and treatment strategies.(2) Despite this emphasis on motor symptomatology, several studies have shown that the non-motor symptoms of Parkinson's disease, such as depression, psychosis, falls, pain, and sleep disturbance, have greater significance when assessed by quality-of-life measures, institutionalizations rates, or health economics.(3) The prevalence of non-motor symptoms as a whole is inadequately documented because there are insufficient adequately powered, community-based studies on prevalence, effect, and treatment efficacy in relation to non-motor symptoms, and there is a need for large and well-designed prospective studies. Non-motor symptoms correlate with advancing age and disease severity, although some non-motor symptoms, such as olfactory problems, constipation, depression and rapid eye movement disorder, can occur early in the disease. PD cannot be diagnosed until motor symptoms appear, but many patients will in hindsight recall a prodromal phase including nonmotor symptoms.

Out of all the nonmotor symptoms, this paper will focus on pain, regarding the pathophysiology, clinical features, epidemiology and treatment.

DEFINITION AND CLASSIFICATION OF PAIN IN PARKINSON'S DISEASE PATIENTS

Pain is defined according to the International Association for the Study of Pain (IASP) as unpleasant sensory and emotional experiences with actual or potential tissue damage or described in terms of such damage. (4)

Many patients with idiopathic Parkinson's disease (PD) experience pain during the course of their disease. Pain can appear in any stage of the disease. In some cases it can appear in the premotor phase of the disease. (5)

Author for correspondence:
Prof. Lacramioara Perju-Dumbrava, MD, PhD, Department of Neurology, "Iuliu Hatieganu" University of Medicine and Pharmacy, 13 Emil Isac Str., Zip Code 400023, Cluj-Napoca, Romania
email: lperjud@gmail.com

TABLE 1. *Premotor features of Parkinson's disease (adapted from Tolosa 2007)*

Premotor symptoms	Related brain structures	Braak staging
Smell loss	Olfactory bulb; anterior olfactory nucleus	1
Depression	Locus coeruleus; raphe nuclei	2
Constipation	Dorsal nucleus of the vagus enteric plexus neurons?	1
REM behavior disorder Excessive daytime sleepiness	Locus coeruleus pedunculopontine nucleus?	2
Other, less well-documented, premotor symptoms: Restless-legs syndrome, anxiety, pain, apathy and fatigue		

In a review of pain in PD, Ford concluded that while previous studies agreed on the prevalence of pain (40%), they disagreed on the proportion of pain in each category. Based on this review, Ford proposed a framework for the classification of pain in PD patients. He described five different categories of IPD-related pain: musculoskeletal pain due to parkinsonian rigidity, rheumatologic disease, or skeletal deformity; radicular-neuropathic pain due to a root lesion, or focal or peripheral neuropathy; dystonic pain related to the timing and dosing of antiparkinsonian medication; central or primary pain related to timing and dosing of antiparkinsonian medication; and akathisia-in an 'off' period or drug induced. (6)

In 1999, Serratrice and Michel concluded that the pathophysiology of pain in PD was complex and poorly understood. They classified pain in PD under the headings of primary (directly caused by PD, such as cramps or paresthesias) and secondary pain syndromes (e.g., postural disorders or osteoarthritis). Therefore, the pain could be PD-related or non-PD-related. (7)

Lee and coworkers published in 2006 a survey of pain in PD. Pain was assessed using quantitative and qualitative tools. (8) Quantitatively, pain was measured using the Palliative Care Assessment Tool (PACA), the Wisconsin Brief Pain Inventory (BPI) and a 100 mm Visual Analogue Scale (VAS). Qualitatively, for each pain, patients were asked about the position, radiation, onset, periodicity (i. e., constant or intermittent), character, associated symptoms, precipitating and relieving factors, and relationship to antiparkinsonian medication. Analgesic use was also collected according to the WHO ladder (Steps 1, 2, and 3 plus adjuvants). (9) After these assessments, pain was classified under the following headings according to cause:

a) Neuropathic or nociceptive pain

b) A new general pain classification based on a model used in cancer care:

- PD-related pain
- PD treatment-related pain (i.e., PD drugs causing pain)
- Pain indirectly related to PD (e.g., pressure sores/injury from falls)
- Pain unrelated to PD
- Other/multiple causes

Pain was considered to be PD-related when it met certain criteria. These were pains that responded to PD treatment; pains that were more prominent on the side maximally affected by PD and that did not have any other clear cause on that side; and pains that matched the descriptions given by Ford in his classification but could not be attributed to any other cause from the medical history.

In the French DoPaMiP Survey (Douleur et maladie de Parkinson en Midi-Pyrenees) chronic pain in PD patients was classified as follows: ''non-PD-pain'' (pain related to another cause than PD and not aggravated by PD) and ''PD-pain'' (pain that was caused or aggravated by PD). In this last category, pain was considered to be (1) directly related to PD (''PD-Pain direct'') if it could not be attributed to any other health problem according to medical history, clinical examination, laboratory test, or imaging results, or (2) indirectly related to PD (''PD-pain indirect'') if another diseases caused pain (e.g. osteoarthritis) but PD aggravated pain intensity because of rigidity, abnormal posture, or movements. (10)

The precise origin of pain and other sensory symptoms that occurs in Parkinson's disease is unknown. Snider and Sandyk have divided these sensory symptoms into two useful categories: 'primary' and 'secondary' symptoms. (10) Primary sensory symptoms are assumed to originate somewhere in the peripheral or CNS; secondary sensory symptoms are caused by edema, dystonia, vascular disorders or muscle cramps and strains. (11,12)

PATHOLOGY OF PAIN IN PD

Some authors consider that the primary pain symptoms which accompany Parkinson's disease are not directly related to motor phenomena for several reasons. (13) First, in some cases, pain is observed contra lateral to the body area with motor

signs. (14) Second, complaints of pain can precede the diagnosis of Parkinson's disease: sensory symptoms can exist for several years before the usual motor symptoms associated with the disorder develop. (14,15,16) Third, the degrees of rigidity, bradykinesia, tremor and posture abnormality are not significantly different in Parkinson's disease patients with pain symptoms compared to those without pain symptoms. (17) Moreover, in some patients, there is no correlation between pain and tremor or rigidity. (18,19) There is also no correlation between nuchal rigidity and nuchal-occipital pain in those Parkinson's disease patients with headache. (20) In contrast to these findings, musculoskeletal pain and dystonia are associated with parkinsonian disability (20). Fourth, in a Parkinson's disease patient with bilateral pain in the legs, an anesthetic block that rendered the leg muscles flaccid did not alleviate the pain. (22) Fifth, motor nerve conduction velocities and somatosensory evoked potentials are often normal in Parkinson's disease. (13,16) Sixth, while antiparkinsonian medication sometimes relieves both motor and pain symptoms, (23) this type of therapy does not always alleviate pain symptoms and in some cases can increase sensory symptoms. (17,23)

Evidence from experimental and clinical studies clearly shows that the basal ganglia participate in processing nociceptive information. Several roles for the basal ganglia in pain sensation are suggested by the (1) neuroanatomical connections of basal ganglia nuclei, (2) electrophysiological response properties of basal ganglia neurons, (3) metabolic and blood flow changes within the basal ganglia following noxious stimulation, (4) altered pain-related behaviors of animals following lesions, electrical stimulation and pharmacological manipulation of the basal ganglia and lastly, (5) pain symptoms that arise after basal ganglia injury.

First, the basal ganglia are likely to participate in the sensory-discriminative aspect of pain by encoding the magnitude of noxious stimulation. The encoding of noxious stimulus intensity by varying neuronal discharge rate may be used to grade the speed or intensity of movement in escaping or avoiding painful stimuli. Since nociceptive basal ganglia neurons do not represent the skin in a discrete topographic fashion (poor spatial localization), they are unlike nociceptive neurons in areas such as the dorsal horn and primary somatosensory cortex which are known to participate in precise localization of noxious stimuli.

Second, a role for the basal ganglia in the affective dimension of pain is probable based on the outcome of electrical stimulation on affective behaviors and the neural connections between the basal ganglia and loci associated with emotional behaviors.

Third, clinical and experimental reports of sensory neglect following basal ganglia injury suggest that the basal ganglia may have role in the cognitive dimension of pain. This role in pain may involve selective attention which can influence coordinated motoric responses to noxious stimuli.

Fourth, since pharmacological, electrical and surgical manipulation of the substantia nigra and striatum can affect behavioral and neuronal responses to noxious stimuli, the basal ganglia may also be involved in the modulating nociceptive information. This modulation most likely occurs within the medial thalamus. Fifth, it is possible that basal ganglia structures provide a gating mechanism for regulation of nociceptive information to higher motor centers. (13)

Other authors noticed that in some patients the pathogenesis of pain appears to be related to central dopaminergic mechanisms and improves in response to dopaminergic medications.

Schestatsky et coworkers performed a psychophysical and neurophysiologic study in 9 PD patients with central pain, 9 patients with PD without pain and 9 healthy control subjects using quantitative sensory testing with thermal probes, and recorded laser-evoked potentials (LEPs) and laser-induced sudomotor skin responses (l-SSRs) in "off" and "on" conditions. They noticed that the conduction along peripheral and central pain pathways was normal in patients with Parkinson disease with or without primary central pain. However, their patients exhibited lack of habituation of sympathetic sudomotor responses to repetitive pain stimuli, suggesting an abnormal control of the effects of pain inputs on autonomic centers. Abnormalities were attenuated by L-dopa, suggesting that the dysfunction may occur in dopamine-dependent centers regulating both autonomic function and inhibitory modulation of pain inputs. (24)

EPIDEMIOLOGY

Pain prevalence in general population in different countries is difficult to compare because of different study designs and inclusion criteria. Variations in pain prevalence in PD have been described in the literature, raging from 38 to 85% (6,8).

The DoPaMiP (Douleur et maladie de Parkinson en Midi-Pyrenees) assessed chronic pain prevalence in a general PD population. 278 (61.8%) of

the 450 parkinsonian patients enrolled in the study reported chronic pain. Among the 278 PD patients with chronic pain, 167 (60.1%) did so, at least partly, because of PD (PD-pain group). In these, no other cause of pain than PD could be identified in 103 (PD-direct group), whereas PD aggravated a pain of other origin in 64 (PD-pain indirect). The other 111 PD patients with chronic pain did do because of another disorder than PD (osteoarthritis in 88/111) with no influence of PD on pain. (10)

In a survey of pain in PD conducted in UK, the authors analyzed 123 patients who reported 285 different pains, giving a mean of 2.3 pains per patient (SD=1.27). 70.7% of patients described two or more different pains, while 22.8% described four or more. Of the 285 pains, 270 (94.7%) were classified as nociceptive. Only 15 (5.3%) were suggestive of a neuropathic mechanism. The most common pains were unrelated to PD and were present in 64.2% of the patients. The pains that were unrelated to PD were most commonly osteoarthritis (73.1%), muscular pain (8.3%), trauma (6.2%) and visceral pain (5.5%). The 121 pains deemed to be PD-related were present in 77 patients (62.6%). The majority of these pains were musculoskeletal (67%) or dystonic (26.4%). Both PD-related and non–PD–related pains coexisted in some cases but were clearly differentiated by patients as different types of pain. (8)

A study conducted in Germany analyzed the prevalence of back pain in PD patients. 101 PD patients and 132 controls completed the questionnaire. 75 of 101 PD patients (74%) had back pain within the last week when compared with 35 of 132 control patients (27%). Radicular pain was present in 38 of 101 PD patients (38%) and in 16 of 132 controls (16%). Pain was constant in 53% of PD patients, but only in 10% of controls ($p< 0.0001$, Fischer exact test). Back pain occurred rarely in 15%, weekly in 17% and daily in 52% of PD patients, while pain occurred rarely in 33%, weekly in 17% and daily in 22% of control patients ($p<0.0001$, chi-square test). (26)

A cross-sectional survey conducted in France in 2006, estimated the extent of back pain on PD patients. The study included 104 idiopathic PD and 100 control patients from the Cardiology and Diabetology department. 62 PD patients (59.6%) reported thoracic or lumbar pain. The point prevalence of pain (59.6%) was significantly higher than that observed in control patients (23%, $p< 0.0001$). The pain was described as chronic by 95.2% of parkinsonians and constant by 56.4%. Pain was statistically more chronic ($p=0.011$) in the PD group than in the control group. (27)

A group from Sweden conducted a study in which they compared the quality of life and pain symptoms in PD patients compared to a matched control group. They observed no statistical differences between duration of pain in patients and controls. 52% of the patients considered that PD had caused pain at some time and one third mentioned musculoskeletal disorders as a reason for pain. (28)

ASSESSING PAIN IN PD

In order to treat pain one has to assess pain and to find factors that might influence its course and progression. One method would be to determine the pain threshold. Brefel-Courbon et al hypothesized that the basal ganglia damage and the dopamine deficit is expected to modify pain perception and activity of several areas involved in nociception and this may result in the occurrence of pain. The aim of their study was to compare the pain threshold before and after the administration of levodopa in PD patients who did not experience pain and in control subjects. A secondary objective of the study was to investigate cerebral activity with PET during experimental nociceptive stimulation and to assess the effect of levodopa on cerebral activity in the two groups of subjects. They included nine PD patients and nine healthy controls. Pain threshold was assessed using thermal stimulation. In the *off* condition, pain threshold in PD patients was significantly lower than in controls (8.0 ± 2.9°C vs.-4.4 ±3.8°C; $P =0.03$) Levodopa (216±50 mg) significantly raised pain threshold in PD patients (8.0±2.9°C vs. 4.6± 3.0°C; $P= 0.007$). By contrast administration of levodopa (200mg) did not significantly change pain threshold in normal subjects (4.4 ±3.8°C vs. 3.0 ±2.0°C; $P= 0.26$). In the on condition, pain thresholds were not significantly different between PD and controls (4.6± 3.0°C vs. 3.0 ±2.0°C; $P =0.19$). This study shows that nociceptive threshold is lower in PD patients without dopaminergic drug than in controls and returns to normal ranges after levodopa administration. Thus, the authors conclude that dopaminergic neurodegeneration may produce hypersensitivity to pain stimuli in several cortical areas. (29)

Vela et al in 2007 examined whether PD patients with dyskinesia had a lower pain threshold than those without dykinesia or non-PD controls. They assessed pressure-pain threshold (PPT) using a hand-held pressure algometer. They observed no

differences in PPT between controls and PD patients with or without dyskinesia. The only significant difference was that women, whether PD or controls, had a lower PPT than men. This was the only study at the time to assess pain threshold using pressure-pain. (30)

Another study used the nociception flexion reflex (RIII) in order to determine pain threshold in PD patients. RIII threshold was lower in patients with PD than in healthy subjects. This observation supports the fact that patients with PD are likely to have abnormal pain thresholds, as suggested by previous studies. (31)

Pain can also be assessed using scales such as: Brief Pain Inventory –short form and VAS scale (0-no pain; 10-worst pain possible).

Another method to assess pain would be to determine the quality of life, as everyone knows this is very much influenced by pain. One well-known generic self-administered HRQL instrument is the Medical Outcomes Study 36-Item Short Form (SF-36). The PDQ-39 is the most widely used Parkinson's Disease specific measure of health status.

TREATMENT OF PAIN IN PD PATIENTS

Pain should be carrefully assessed before any treatment is given to the patient in order to determine its possible ethiology and the degree of nociceptive and neurogenic characteristics.

Notwithstanding the uncertainties about the type of pain and its underlying mechanisms, there is still an urgent need for pain relief. The first and most evident measure is to maximally reduce motor symptoms with anti-parkinsonian medication. (32)

When the pain fluctuates in parallel with the motor changes, this pain may respond to modifications in anti-parkinsonian therapy, which can be far more effective than conventional analgesic treatments (33)

In an article published in 2006 by Lee and coworkers it is reported that the use of analgetics according to the WHO ladder was 58.5% (8) (see TABLE 2).

This was the first study to document analgesic use, therefore the first to highlight their underused in an IPD population. Given the fact that most of the pains experienced by the patients in this study were intermittent (83.9%) it was not surprising that 41.5% of the patients were on no analgesics. However when the authors looked at patients who reported moderate to severe constant pain or pain dominating their day, they noticed that 23.3% and 20% respectively, were on no analgesics. Also, patients who were older (over 85 years) or cognitively impaired were less likely to receive analgesics.

Before embarking on regular conventional analgesics, it is useful to optimize dopaminergic therapy and physiotherapy input. Most patients in this study managed cramps with physical interventions, such as stretches, massage, or mobilizing.

The French study DoPaMiP assessed analgesic consumption in PD patients. Almost 50% of the parkinsonian patients took at least one analgesic during the previous month. The analgesic use was lower than that of patients with no-PD pain. This lower level of analgesic consumption may reflex the lower frequency with which patients reported PD-pain to their physicians, as opposed to non-PD-Pain. The authors recon that a poor understanding of the mechanisms underlying pain raised doubts about analgesic efficacy in this situation, or that other types of management, such as dopaminergic drug adjustment, were preferred. (10) (see TABLE 3)

Breffel-Courbon and coworkers published in 2009 in Pain the largest study concerning chronic analgesic drug consumption in PD patients compared to other chronic diseases (diabetes and osteoarthritis) and to the general population. 11466 PD

TABLE 2. *Use of analgesics in PD patients (Adapted from Lee et al, 2006)*

WHO Ladder	Drug	%
Step 1	NSAID Paracetamol/acetaminophen	12.2 50.4
Step 2	"Weak" opioids	25.2 (most commonly codeine)
Step 3	"Strong" opioids	0
Adjuvant analgesic	Anticonvulsants Antidepressants Steroids Muscle relaxants	0.8 8.9 0 0.8

TABLE 3. *The use of analgesics in PD patients (Adapted from DoPaMiP Survey 2008)*
**p<0.005; **p<0.01: PD pain versus non PD-pain*
##p<0.01; ###p<0.001; PD pain versus patients with disorders other than PD and chronic pain

	PD-pain (n=167)	Non-PD pain (n=111)	Patients with disorders other than PD and chronic pain (n=57)	P value
Any analgesic	50.3% (43-58)**,##	67.6% (59-76)	70.2% (58-82)	0.003
Level I	34.1% (27-41)*,###	48.6% (39-58)	61.4% (49-74)	0.0007
Level II	9.6% (5-14)	15.3% (9-22)	10.5% (3-19)	0.33
Level III	0.6% (0-2)	0	0	-
Co-analgesic	10.8% (6-16)	16.2% (9-23)	15.8% (6-25)	0.36

patients, 11459 diabetics, 11359 patients with osteoarthritis and 11200 subjects in the general population were included. (34) Diabetic patients were considered to have mostly neuropathic pain, while patients with osteoarthritis were considered to have nociceptive pain. These are the two main types of pain in PD patients. Analgesic drug prescription is considered a reliable tool for an estimation of prevalence of pain.

The authors noticed that PD patients significantly received more prescription of analgesics than the general population (82% versus 77%, p<0.0001) and fewer than patients with osteoarthritis (82% versus 90%, p< 0.0001). There was no significant difference in analgesic drug prescription between PD and diabetic patients.

Prescriptions of specific analgesics (opiates and other analgesics such as acetaminophen) in PD patients were higher than in the general population, similar to diabetics and less important than in patients suffering from osteoarthritis. Osteoarthritis patients were the most important users of NSAIDs. Prescriptions of other analgesics (antidepressants and antiepileptics) were significantly more observed in PD patients than in all groups of control. (34)

TABLE 4. *Analgesic drug prescription (acute/chronic) (Adapted from Brefel-Courbon, 2009)*
**Difference between PD patients and control populations (versus general population, versus Diabetic and versus Patients with osteoarthritis) was statistically significant at the level 0.05. Statistics are only presented for class of drugs*

Variables	Control populations			
	PD patients (n=11466)	General population (n= 11200)	Diabetics (n=11459)	Patients with osteoarthritis (n=11329)
Reimbursement of at least one prescription of analgesics	81.9	76.6*	81.5	88.9*
Reimbursement of at least one prescription of analgesics by class				
Opiates	38.8	32.2*	37.4	43.0*
Tramadol	13.3	9.6	12.1	14.0
Dextropropoxyphene	28.9	25.0	28.6	33.4
Morphine	2.1	1.4	1.6	1.1
Codeine	4.3	3.3	4.5	4.5
Fentanyl	2.6	1.1	1.4	0.9
Other analgesics	65.8	61.4*	66.9	70.2*
Acetaminophen	64.2	59.0	64.7	68.1
Antiepileptics	14.9	6.0*	7.0*	6.2*
Gabapentine	2.9	1.5	2.1	1.3
Clonazepam	10.3	3.7	4.6	4.4
Carbamazepine	0.9	0.7	0.6	0.6
Antidepressants	6.6	2.8*	3.0*	2.9*
Amitriptyline	4.5	2.1	2.3	2.3
Clomipramine	2.2	0.8	0.7	0.6
NSAIDs	34.0	36.2*	36.4*	52.4*

After all these studies, one still wonders what the outcome of using analgesics in PD is. Unfortunately, no controlled trial has been reported on this subject. This is the case, even though most neurologists consider it difficult to treat pain associated with PD.

In conclusion Parkinson's disease should be considered as a painful disease, but still many questions about the origin and treatment of pain remain to be answered in future studies.

REFERENCES

1. **Parkinson J.** An essay on the shaking palsy (reprint of monograph published by Sherwood, Neely, and Jones, London, 1817). *J Neuropsychiatry Clin Neurosci* 2002; 14: 223–36.
2. **Chaudhuri KR, Healy DG, Schapira AHV.** Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurology* 2006; 5: 235-45
3. **Chaudhuri KR, Yates L, Martinez-Martin P.** The non-motor symptom complex of Parkinson's disease: time for a comprehensive assessment. *Curr Neurol Neurosci Rep* 2005; 5: 275–83.
4. **IASP Pain Terminology (cited 2009 March 5).** Available at URL: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions&Template= /CM/HTMLDisplay.cfm&ContentID=1728#Pain
5. **Tolosa E, Compta Y, Gaig C.** The premotor phase of Parkinson's disease. *Parkinsonism and Related Disorders* 2007; 13: S2–S7.
6. **Ford B.** Pain in Parkinson's disease. *Clin Neurosci* 1998; 5: 63-72.
7. **Serratrice G, Michel B.** Pain in Parkinson's disease patients. *Rev Rhum Engl Ed* 1999; 66: 331-338.
8. **Lee MA, Walker RW, Hildreth TJ, Prentice WM.** A survey of pain in Idiopathic Parkinson's disease. *J Pain Symptom Manage* 2006; 32: 462-469.
9. **World Health Organization.** Cancer pain relief. Geneva: *World Health Organization*, 1986.
10. **Chronic Pain in Parkinson's Disease:** The Cross-Sectional French DoPaMiP Survey. *Movement Disorders* 2008; 10 (23):1361–1369
11. **Snider SR, Sandyk R.** Sensory Dysfunction. In W.C. Koller (Ed.), *Handbook of Parkinson's Disease*, Marcel Dekker, New York, 1987, 171-180.
12. **Itson J, Fahn S, Cote L.** Painful dystonic spasms in Parkinson's disease, *Adv Neuro*.1984; 40: 395-398.
13. **Chudler EH, Dong WK.** The role of the basal ganglia in nociception and pain. *Pain* 1995; 60: 3-38
14. **Koller WC.** Sensory symptoms in Parkinson's disease. *Neurology* 1984; 34: 957-959.
15. **Sandyk R.** Back pain as an early symptom of Parkinson's disease. *S Aft Med J* 1982; 61: 3.
16. **Koller WC.** When does Parkinson's disease begin. *Neurology* 1992;42 (S4): 27-31
17. **Snider SR, Fahn S, Isgreen WP, Cote LJ.** Primary sensory symptoms in parkinsonism. *Neurology* 1976; 26: 423-429.
18. **Schott GD.** Pain in Parkinson's disease. *Pain* 1985: 407-411.
19. **Urakami K, Takahashi K, Matsushima E, Sano K, Nishikawa S, Takao T.** The threshold of pain and neurotransmitter's change on pain in Parkinson's disease. *Jpn. Psychiat Neurol* 1990; 44: 589-593.
20. **Indo T, Naito A, Sobue I.** Clinical characteristics of headache in Parkinson's disease. *Headache* 1983; 23: 211-212.
21. **Goetz CG, Tanner CM, Levy M, Wilson RS, Garron DC.** Pain in Parkinson's disease. *Movement Disorders* 1986; 1: 45-49.
22. **Sage JI, Kortis H, Sommer W.** Evidence for the role of spinal cord systems in Parkinson's Disease-associated pain. *Clin Neuropharmacol* 1990; 13: 171-174.
23. **Quinn NP, Koller WC, Lang AE, Marsden CD.** Painful Parkinson's disease, *Lancet*, 1986; 1: 1366-1369.
24. **Schestatsky P, Kumru H, Valls-Sole J, Valldeoriola F, Marti MJ,Tolosa E et al.** Neurophysiologic study of central pain in patients with Parkinson disease. *Neurology* 2007;69 (23): 2162-2169
25. **Lees AJ.** A sustained-release formulation of L-dopa (Madopar HBS) in the treatment of nocturnal and early-morning disabilities in Parkinsons disease. *Eur Neurol* 1987; 27: S126-S134.
26. **Broetz D, Eichner M, Gasser T, Weller M, Steinbach JP.** Radicular and Nonradicular Back Pain in Parkinson's Disease: A Controlled Study. *Movement Disorders* 2007, 22 (6): 853–856.
27. **Etchepare F, Rozenberg S, Mirault T, Bonnet A-M, Lecorre C, Agid Y, et al.** Back problems in Parkinson's disease: an underestimated problem. *Joint Bone Spine* 2006; 76: 298–302.
28. **Quittenbaum BH, Grahn B.** Quality of life and pain in Parkinson's disease: a controlled cross-sectional study. *Parkinsonism and Related Disorders* 2004; 10: 129–136.
29. **Brefel-Courbon C, Payoux P, Thalamas C, Ory F, Quelven I, Chollet F, et al.** Effect of Levodopa on Pain Threshold in Parkinson's Disease: A Clinical and Positron Emission Tomography Study Movement Disorders 2005; 20 (12): 1557–1563.
30. **Vela L, Lyonsb KE, Singerc C, Lieberman AN.** Pain–pressure threshold in patients with Parkinson's disease with and without dyskinesia. *Parkinsonism and Related Disorders* 2007; 13: 189–192.
31. **Gerdelat-Mas A, Simonetta-Moreau M, Thalamas C, Ory-Magne F, Slaoui T, Rascol, Brefel-Courbon C.** Levodopa raises objective pain threshold in Parkinson's disease: a RIII reflex study. *J Neurol Neurosurg Psychiatry* 2007; 78;1140-1142.
32. **Boivie J.** Pain in Parkinson's Disease. Editorial. *Pain* 2009;141:2-3.
33. **Quinn NP, Koller WC, Lang AE, Marsden CD.** Painful Parkinson's disease. *Lancet* 1986;1(8494):1366-9.
34. **Brefel-Courbon C, Grolleau S, Thalamas C, Bourrel R, Allaria-Lapierre V, Loï R et al.** Comparison of chronic analgesic drugs prevalence in Parkinson's disease, other chronic diseases and the general population. *Pain* 2009; 141: 14–18.