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MODERN APPROACHES TO THE TREATMENT OF NON-MOTOR SYMPTOMS IN PARKINSON'S DISEASE

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Parkinson's Disease (PD) is a chronic progressive brain disorder primarily associated with the degeneration of dopaminergic neurons in the substantia nigra, accompanied by the formation of specific intracellular inclusions (Lewy bodies). It manifests as a combination of hypokinesia with rigidity, resting tremor, and postural instability [1,2,3,8].

In addition to characteristic motor symptoms, PD also affects other brain structures, including brainstem nuclei, the limbic system, and various cortical areas. This leads to a wide range of non-motor symptoms, which have an impact on a patient's daily life that is no less significant than motor impairment. Non-motor symptoms may precede the development of the classical motor symptoms of the disease and can also be an integral part of its clinical picture.

Non-motor symptoms of PD include psychiatric, autonomic, sleep-related, sensory, and other disorders [2,5,8,10,13]. One of the most common disorders observed in PD patients is depression. According to various studies, depression occurs in 4% to 90% of PD patients, with an average prevalence of 40% to 50% [3,4,9]. The risk of developing depression in PD patients is approximately twice as high as in individuals of the same age and sex without PD [3,13].

The severity of depressive symptoms varies widely. In most patients, depression is mild to moderate, while in a comparatively small proportion of patients (4%–22%), it is severe [3,4,9]. Depression can emerge during the prodromal phase, years or even decades before the onset of motor symptoms, and may persist throughout the course of the disease [3,9,13].

Chronic pain is even more prevalent in PD than depression, occurring in 69%–84% of patients [7,8,10,12,13]. There is a clear association between pain and depression, as PD patients with depression are twice as likely to experience pain compared to those without depression. However, despite this, individuals with PD are less likely to take painkillers and even less likely to receive antidepressants.

Pain in PD may have a central origin, be musculoskeletal, orofacial, or occur in the limbs. Pain associated with motor fluctuations and dyskinesias, along with central pain, is likely directly linked to PD itself and may be classified as parkinsonian pain. Other forms of pain are secondary and not directly related to PD as a disease entity.

The purpose of our study was to investigate the effectiveness of using the dopamine receptor agonist – pramipexole compared with the antidepressant duloxetine for the treatment of pain syndrome and depression, motor fluctuations in PD.

We examined 34 patients (21 women and 13 men) aged from 54 to 65 years with a diagnosis of Parkinson’s disease. Diagnosis verification was carried out in accordance with the international clinical diagnostic criteria of the United Kingdom Parkinson’s Disease Society Brain Bank.

Disease stage was assessed according to the Hoehn and Yahr scale (Hoehn, Yahr, 1967) modified by Lindvall (1989), Tetrud, Langston (1989) from stage 1 to 2.5. Among them were: 12 persons - stage 1-1.5, 13 persons - stage 2, 9 persons - stage 2.5. The most frequently occurring was the rigid-tremor form - in 19 persons, the akinetic-rigid form - in 15 persons.

The severity of non-motor manifestations was determined using the Unified Parkinson's Disease Rating Scale (UPDRS) - part I for evaluating non-motor manifestations of the disease in daily life [13].

All patients received traditional combined antiparkinsonian therapy in the form of levodopa and amantadine preparations.

Patients presented complaints of pain sensations localized in the neck muscles (70.5%), shoulder joint (41.2%), the localization of pain was most pronounced on the affected side. The pains were associated with PD symptoms, unilateral rigidity, and bradykinesia. Stiffness in the limbs (67.6%) and slowness of walking, limitation of joint mobility were noted, leading to pronounced painful spasms (44.1%) and tension in the muscles of the neck, shoulder, paravertebral musculature (61.8%).

Pain intensity varied during the "on" period and/or during dyskinesias. Changes in pain intensity were associated with the intake of antiparkinsonian medications. To

assess the severity of pain, a visual analog scale (VAS) was used. Pain syndrome was observed in all 34 patients, with varying intensity, and the duration of pain was more than 3-6 months.

The presence of mild and moderate depression was noted in 28 patients, manifesting as depressed mood (85.7%), anhedonia (67.9%), decreased appetite (39.3%), changes in body weight (32.1%), rapid fatigue (82.1%), sleep disturbances (57.1%), low self-esteem (42.9%), increased anxiety (92.9%), irritability (64.3%), pessimistic thoughts about the future.

The severity of depression was determined using the Hamilton Rating Scale, which is one of the most sensitive for this disease [3,11]. For screening diagnosis of depression in PD, a total score exceeding 11 points is considered sufficient.

The total Hamilton Rating Scale score in these patients averaged 15.1±1.6. In all patients of this group, depression was combined with pain syndrome. A relationship between pain intensity and severity of depression was also noted.

Considering that dopamine receptor agonists reduce the severity of motor fluctuations and also have a good antidepressant effect, 14 patients were prescribed pramipexole according to a regimen at an average therapeutic dose of 1.5 mg, in addition to the main therapy.

The remaining 12 patients were prescribed the antidepressant duloxetine, a serotonin-norepinephrine reuptake inhibitor, at a daily dose of 60 mg, which has an analgesic effect and is used to treat chronic pain syndrome.

The duration of treatment in both groups was 12 weeks.

Patients receiving pramipexole noted a reduction in pain severity during the "on" period by an average of 57.1%, which might largely be associated with the antidepressant effect of the drug. Pain intensity decreased to a lesser but still significant extent by 35.7% during the "off" period. The severity of depressive symptoms decreased by the end of the 12th week of pramipexole administration from 15.1±2.3 to 10.3±3.4 points.

After a course of treatment with duloxetine at a daily dose of 60 mg, pain severity also decreased in 8 out of 12 patients (66.7%). As early as the 10th day, patients reported a reduction in pain and stiffness of movements, and the severity of pain syndrome according to the VAS scale decreased from 6.2 ± 0.8 to 3.0 ± 0.5 ($p < 0.1$); however, these indicators were not directly related to motor fluctuations in PD. They were more associated with the presence of myofascial and vertebrogenic syndromes. The severity of depressive symptoms correlated with pain syndrome and decreased to 9.8±3.1 points by the end of the 12th week of duloxetine administration.

Thus, it can be argued that there is a definite relationship between pain and motor complications in PD. Pain intensity correlates with the severity of depression. The use of duloxetine demonstrated good efficacy in PD patients with chronic myofascial pain syndrome, neuropathic pain, and vertebrogenic pain syndromes, reducing pain syndrome and depression severity, but having a lesser impact on motor symptoms in Parkinson's disease.

Considering its antidepressant effect and ability to reduce motor complications and consequently pain syndrome, the dopamine receptor agonist pramipexole remains the drug of choice in patients with Parkinson's disease with non-motor manifestations in the form of depression and pain.

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