

MODERN APPROACHES TO THE TREATMENT OF PSYCHOTIC DISORDERS IN PARKINSON'S DISEASE

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Psychotic disorders in Parkinson's disease (PDPD) are observed in a large number of patients. They have a significant impact on the quality of life and the level of disability. The pathogenesis of PDPD is complex and not fully understood. Taking into account the specificity of PD (usually elderly patients with a risk of cognitive impairment), as well as the pharmacodynamic features of antiparkinsonian and classical antipsychotic drugs, the treatment of PDPD requires special attention from neurologists and psychiatrists. This systematic review summarizes the results of scientific publications for the period 2014-2016 in two bibliographic databases: MEDLINE/PubMed and eLIBRARY.RU, as well as clinical guidelines of the International Parkinson's Disease and Movement Disorders Society, the American and European Academies of Neurology. Of the antipsychotic drugs, clozapine is a drug recommended for use, quetiapine is a drug that is recognized as possible for use, pimavanserin is likely to become one of the drugs of choice in the treatment of PDPD. Non-pharmacological treatments have shown positive effects in terms of improving the general condition of patients with PD, but their effectiveness in treating PD itself remains unclear.

Key words: Parkinson's disease, psychotic disorders, systematic review.

Parkinson's disease (PD) is a multifactorial and multisystem neurodegenerative disorder manifested by motor and non-motor disorders [1, 2]. Non-motor disorders in PD include a wide range of disorders: mental disorders (psychosis, depression, cognitive impairment, etc.), sensory disorders, asthenia, sleep disorders, autonomic and gastrointestinal dysfunctions, behavioral reactions caused by treatment with dopaminergic drugs, and non-motor fluctuations [3]. Psychoses (psychotic disorders in PD - PDPD) are observed in 50-70% of PD patients [4, 5]. Their frequency and severity correlate with the duration of PD, therefore PDPD are typical for late stages of the disease [6, 7]. PDPD have a negative impact on the quality of life of patients and their relatives and the level of disability [8, 9, 10]. Taking into account the specificity of the underlying disease, the risk of cognitive

impairment, especially in elderly patients, as well as the features of the mechanism of action of antiparkinsonian and classical antipsychotic drugs (their opposite effects on the dopaminergic mediator system), the treatment of PRBP requires special attention from neurologists and psychiatrists. Treatment of PRBP in such patients carries a risk of complications: for example, careless administration of typical antipsychotic drugs to a patient with PD can cause a dramatic deterioration in motor symptoms [11, 12]. Thus, the issues of timely detection of PRBP, their risk factors and the choice of therapeutic tactics are relevant in the clinic of both extrapyramidal diseases and mental disorders. This systematic review presents an analysis of scientific publications from 2014-2016, as well as clinical recommendations of authoritative specialized medical organizations regarding the problems of treating PRBP.

Diagnosis of PD In 2007, the expert group of the National Institute of Neurological Disorders and Stroke (USA) formulated the following criteria for PD [13, 14]: constant or intermittent occurrence of at least one of the following symptoms: hallucinations, a sense of the presence of another person, illusions, or delusions for at least 1 month in a patient meeting the clinical diagnostic criteria for PD (criteria of the Brain Bank of the UK PD Society [15, 16]). These psychotic symptoms develop after the onset of PD in the absence of another explanation for these symptoms (dementia with Lewy bodies or primary mental illness, delirium, schizophrenia). Dementia is considered a generally accepted risk factor for PD [17]. It has also been noted [18, 19] that the risk is higher in the presence of visual impairment, depression, age over 65 years at the onset of PD, longer duration of PD, rapid eye movement sleep phase disorders, axial motor disorders, and treatment with dopamine agonists. Immediate trigger factors and factors aggravating PD are infections, dehydration, stress, intake of amantadine, anticholinergics, and β -blockers [20, 21]. Before the introduction of levodopa into practice, mental disorders were rarely observed in patients with PD [22], so it was traditionally believed that treatment with antiparkinsonian drugs and dementia were the main causes of PD [23, 24]. However, the results of subsequent studies [25] have questioned this assumption. Currently, PD is believed to be caused by a combination of external and internal factors [26, 27]. In addition to the influence of dopaminergic drugs, modern concepts of the pathogenesis of PDBP also attach great importance to dysfunctions of the cholinergic [28] and serotonergic [29, 30] neurochemical systems of the brain and organic changes in the brain [31, 32].

Types of PDBP The following types of PDBP are most frequently encountered in clinical practice: hallucinations, illusions, and delusional disorders. Hallucinations are the most typical symptom of PDBP. In most cases, they are visual, less often auditory. Unlike schizophrenia, hallucinations in PDBP do not have an emotional

component [33], are stereotypical, repetitive, and occur more often in the evenings when the PD patient is alone in a room reading a book or watching television [34, 35]. Their content, as a rule, is the same people in the same clothes, performing the same actions [36]. Very often, the so-called feeling of "presence" is observed: the patient feels that there is a stranger in the room with him, who is "hiding" behind furniture or under the bed. A mild form of PRBP is illusions: patients see faces in the branches and leaves of trees, people and animals in household objects [37]. Delusional disorders in PD often occur according to the paranoid type [38]. Delusions of reference, damage, depersonalization, Capgras syndrome (delusion of a negative double), Fregoli (positive double) and Othello (jealousy) are noted [39, 40]. Literature search methods In order to analyze recommendations and expert opinions on the treatment of PRBP, a search query was performed in two bibliographic databases: MEDLINE/PubMed [41] and eLIBRARY.RU (an electronic library of scientific publications integrated with the Russian Scientific Citation Index) [42]. PubMed search criteria: full-text publications in peer-reviewed journals in English for the period from January 2014 to April 2016, by the combination of keywords [psychosis] and [parkinson*] in the article title and abstract; query code: ((psychosis[Title/Abstract]) AND parkinson*[Title/ Abstract]) AND («2014»[Date — Publication] : «2016»[Date — Publication]). eLIBRARY.RU search criteria: full-text publications in peer-reviewed journals in Russian for the period from January 2014 to April 2016, by the combination of keywords [psychosis] and [parkinson*] in the article title and abstract, on the topic «Medicine and Healthcare», taking into account morphology. The inclusion criterion for the full-text analysis was the availability of data on methods of treating PDSD (pharmacological and non-pharmacological). Clinical guidelines of the following organizations were also analyzed: the American Academy of Neurology (AAN) [43], the European Academy of Neurology (EAN) [36], and the International Parkinson Disease and Movement Disorders Society (IPMDS) [44]. The final full-text analysis included 16 scientific publications. The search and selection algorithm for publications is presented in Table 1.

Results

Based on the analysis of the selected sources, recommendations for the treatment of PRBP were formulated. If PRBP is detected: moderate mental symptoms (illusions, a sense of presence) that do not significantly impair the patient's quality of life and social activity, while maintaining criticality, with a satisfactory general condition require only observation [45, 46]. If PRBP requires treatment: general measures should be taken immediately.



General measures include restoring the sleep-wake pattern (circadian rhythm), restoring an adequate level of sensory stimuli (using visual and auditory stimuli, increasing the amount of light in the room where the patient is), and, if possible, restoring adequate psychosocial contact with family and friends [47]. Most of these measures will have a positive effect regardless of the cause and severity of PRBP. The subsequent treatment tactics are step-by-step.

First stage

Exclusion of trigger factors for PRBP, which include concomitant infections (usually of the bladder, lungs), metabolic disorders, dehydration and intoxication [48, 49]. U. Akbar and J. Friedman [50] recommend performing the following types of clinical examinations at this stage for all patients with PRBP: complete blood count, complete urine analysis, chest X-ray.

Second stage

Reduction of the dose and/or discontinuation of psychoactive drugs not directly related to the treatment of motor disorders of BP. As a rule, these are anticholinergic drugs used for bladder dysfunction, as well as sedatives, benzodiazepines, anxiolytics, opioid drugs [51].

Third stage

Sequential reduction and withdrawal of antiparkinsonian drugs according to the principle of maximum reduction while maintaining patient tolerance of PD motor disorders. Dose reduction and drug withdrawal occur until mental symptoms improve or intolerance to motor disorders develops in a certain sequence (from first to last): anticholinergics, amantadine, dopamine agonists, MAO inhibitors, COMT inhibitors, levodopa [52, 53].

The fourth stage

Prescribing atypical antipsychotic drugs

Pharmacological treatment of PRBP is carried out on an off-label basis, i.e. for indications not approved by specialized regulatory agencies. However, based on RCTs, a number of drugs are included in the clinical guidelines of the International Society of Cardiology and the American Academy of Sciences and the European Academy of Sciences for the treatment of PRBP (Table 2). Clozapine is a first-line drug recommended for the treatment of PRBP, with proven efficacy but with a risk of agranulocytosis. Despite the fact that the



doses of clozapine used in the treatment of PRBP are much lower than those used to treat schizophrenia (300-900 mg/day), the risk of agranulocytosis does not depend on the dose [54]. Therefore, the administration of clozapine requires strict monitoring of the patient's hemogram parameters. Quetiapine is a drug with unclear efficacy (conflicting results of randomized clinical trials), but with a lower risk. Pimavanserin is a 5-HT_{2A} serotonin receptor agonist with virtually no affinity for dopamine receptors. In RCTs, it has shown high efficacy (compared to quetiapine) with minor (compared to clozapine) side effects [41, 48]. In April 2016, pimavanserin was approved by the Food and Drug Administration (FDA) for use in the treatment of PRP [55]. Despite promising results in studies, it should be noted that the maximum therapeutic effect of this drug is manifested after approximately 1 month, and in patients with cognitive impairment, the treatment efficacy is lower than in those with preserved cognitive functions [56, 57] (Table 3). Other antipsychotic drugs are not recommended for use in the treatment of PPD due to their negative impact on motor functions (blocking dopamine receptors) and/or unclear efficacy [58, 59]. It should be added that in elderly patients with psychosis due to dementia, an increased risk of mortality from cardiovascular diseases and infections was noted when treated with antipsychotics compared with placebo [60].

Electroconvulsive therapy (ECT)

Some authors recommend ECT for the treatment of PDBP refractory to antipsychotic drugs [61, 62]. The effectiveness of ECT in the treatment of PDBP has been noted in studies with a small number of patients, as well as in the results of individual clinical cases [63, 64].

Psychotherapy

The effectiveness of psychotherapeutic coping strategy for hallucinations in PD was studied in one study [65, 66]. Cognitive, interactive and visual methods were used. Despite the decrease in the intensity of hallucinations, no significant effect was noted. The feasibility of psychotherapy in the treatment of PD (in particular, mild forms) requires further study [67, 68]. Thus, based on the above, the following conclusions can be made. Of all the antipsychotic drugs, only clozapine is recommended for use for the pharmacological treatment of PD in all sources found. Quetiapine is mentioned as a drug that can be used. It should be noted that, according to the results of RCTs, clozapine is highly effective, but is not widely used due to the risk of side effects and the complexity of



monitoring, while quetiapine, which has insufficient effectiveness, is used much more widely due to its better safety [69,70]. Pimavanserin will likely become one of the drugs of choice for the treatment of PD, but additional RCTs and experience with clinical use will allow a more accurate prediction of its efficacy and safety. Non-pharmacological treatments have a positive effect in terms of improving the general condition of patients with PD, but their effectiveness in treating mental disorders in patients with PD remains unclear. This unsatisfactory situation emphasizes the need for further research to find optimal treatments for PD.

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