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# Use of the Dopamine Receptor Agonist Mirapex in the Treatment of Parkinson's Disease

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We present a review of the literature on dopamine receptor agonists along with our own data on the treatment of Parkinson's disease (PD) with Mirapex, which was used in 30 patients (mean age 61.8 ± 7.7 years, duration of disease 8.4 ± 1.3 years). Mirapex was used at a dose of 3.5 ± 1.1 mg/day on the background of treatment with levodopa preparations. The efficacy of Mirapex was assessed using quantitative scales. Improvements were demonstrated in general state, motor activity, daily activities, and the quality of life. Attention is drawn to a decrease in the severity of motor fluctuations and dyskinesias and in anxiety and depression, and to improvements in cognitive functions. The significance of the combination of the high efficacy and good tolerance of this agent is emphasized.

**KEY WORDS:** Parkinson's disease, treatment, dopamine receptor agonists, Mirapex.

The medical treatment of Parkinson's disease (PD) is directed to stopping and minimizing the neurodegenerative process in nigrostriatal neurons (neuroprotective therapy) and eliminating the biochemical imbalance (symptomatic therapy). The main directions of symptomatic therapy in PD are: 1) to increase dopamine synthesis; 2) to provide direct stimulation of dopamine receptors; 3) to stimulate dopamine release from the presynaptic space; 4) to inhibit dopamine reuptake by presynaptic receptors; and 5) to inhibit dopamine catabolism.

The gold standard in the pharmacological treatment of PD is provided by DOPA-containing substances (DCS) [3, 5, 14, 40]. However, the efficacy of these agents decreases over periods of years because of continuing degeneration of neurons in the substantia nigra. As this process continues, there is a decrease in the level of DOPA decarboxylase, an enzyme required for dopamine synthesis. In the late stages of PD, dopamine circulation in synapses gradually decreases and becomes more fluctuating in nature. The potential of treatment with levodopa preparations also decreases in the late stages of the disease because of side effects and the appearance of motor fluctuations and therapeutic dyskinesias [1, 4, 6, 13, 25, 44, 54, 57]. After constant use of DCS for five years, dyskinesias develop in 68% of patients, with clinically significant motor fluctuations present in 50%. Their genesis includes roles for oscillations in plasma levodopa levels, with progressing degeneration of nigrostriatal neurons, denervation of the striatum, and changes in the functional state and sensitivity of dopamine receptors [4, 6, 8, 9, 25]. The most frequent variants of motor fluctuations in PD are loss of the effect of single doses of DCS, the on/off effect, and rigidity [4, 13, 25, 37]. Dyskinesias are divided into two types: the "peak" type, appearing at the maximum effect of DCS, and the "trough" type, appearing at the minimum of the effect of DCS. The former are often choreoathetoid in nature, while the latter are generally dystonic but may also be choreoathetoid [24, 25, 27].

A fundamentally new class of therapeutic agents with actions directed to countering decreases in dopaminergic activity is provided by the dopamine receptor agonists (DRA). These have the ability to stimulate dopamine receptors in the brain, with selective actions on dopamine receptor subtypes. The pharmacological effects of these agents

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TABLE 1. Actions of DRA on Dopamine Receptors of Different Types

| Agent | $D_1$ | $D_2$ | $D_3$ | $D_4$ | $D_5$ |
|---|---|---|---|---|---|
| Mirapex | – | +++ | +++ | ++ | + |
| Piribedil | – | +++ | +++ | ++ | + |
| Bromocriptine | – | ++ | + | + | + |
| Lisuride | +/– | ++ | ++ | ++ | ? |
| Pergolide | + | +++ | +++ | +++ | + |
| Cabergoline | + | ++ | ++ | + | ? |
| Ropinirol | – | ++ | +++ | ++ | ? |

"bypass" the degenerating nigrostriatal neurons and are not associated with the conversion of levodopa into dopamine. DRA consist of a chemically diverse group of agents, whose interaction with receptors is mediated by insertion of part of the molecular structure which is chemically similar to dopamine.

The first agent of the DRA class – apomorphine – started to be used in the 1950s; the second – bromocriptine – came into use in the early 1970s in combination with levodopa in the late stage of the disease. However, recent years have seen the wide use of agents of this group as monotherapy in the early stages of PD, because of their good clinical effects and presumed neuroprotective actions; DRA combine well with amantadine, selegiline, and cholinolytics [15, 56]. There have in recent years been increasing numbers of randomized multicenter studies on the efficacies of various different DRA (bromocriptine, pergolide, Mirapex, ropinirol, cabergoline, and others) in comparison with levodopa in different stages of PD. The results of these studies show that the use of DRA in different stages of PD is associated with the later appearance of dopaminergic complications as compared with levodopa, and with the delayed appearance of motor fluctuations (deterioration syndrome, on/off) and therapeutic dyskinesia. These points are related to the longer-lasting stimulation of dopamine receptors by DRA as compared with the non-physiological "pulsatile" stimulation of receptors resulting from use of levodopa agents with short elimination half-lives [11, 16, 19, 21, 28, 31, 41, 42, 58].

The effects of DRA depend on the type of dopamine receptors with which they interact. Traditionally, two main types of these receptors are recognized – $D_1$ and $D_2$ – while more recent molecular-genetic methods have allowed no less than five subtypes of dopamine receptor to be identified; several have the pharmacological properties of $D_1$ receptors ($D_1$, $D_5$), while others have the properties of $D_2$ receptors ($D_2$, $D_3$, and $D_4$). Dopamine receptor subtypes have different locations on the pre- and postsynaptic membranes and different sensitivities to endogenous dopamine and DRA. Receptors of the $D_2$ subtypes are located on cholinergic and GABAergic neurons in the striatum and on dopamine neurons in the substantia nigra. $D_1$ receptors are located on striate neurons which send projections to the reticular part of the substantia nigra. The antiparkinsonism effect is associated with stimulation of $D_2$ receptors. Dopaminergic neurons have presynaptic autoreceptors which influence the activity of the neuron and its dopamine synthesis and release. The role of autoreceptors is associated with subtypes $D_2$ and $D_3$. Activation of these receptors has been suggested to be linked with the neuroprotective effects of DRA [11]. The actions of DRA on different types of receptors are shown in Table 1.

DRA are divided into two groups – ergoline and non-ergoline (Table 2). Ergoline derivatives have a much higher incidence of peripheral side effects (erythromelalgia, pulmonary and retroperitoneal fibrosis, Reynaud's syndrome). The most typical side effects of all DRA are nausea, vomiting, dyspepsia, postural hypotension, cardiac arrhythmias, along with central effects consisting of hallucinations and psychoses, sleep disturbances, and episodes of daytime drowsiness [26, 59]. The use of domperidone in the initial period of treatment with DRA (usually the first two weeks) decreases the severity of nausea. It is important to note that psychotypic disturbances are encountered more frequently in aged and elderly patients with marked cognitive impairments.

It is important to emphasize that the halflives of latest-generation DRA are 3–4 times longer than those of standard levodopa preparations (Table 3). This results in longer-lasting stimulation of dopamine receptors and prevents the development or decreases the severity of motor fluctuations and therapeutic dyskinesias associated with variations in blood levodopa concentrations and changes in dopamine receptor sensitivity.

***Mirapex (pramipexole)*** is a synthetic benzothiazole derivative which acts predominantly on $D_3$ (subtype $D_2$) receptors and is highly effective.

Experimental studies have demonstrated that the affinity of Mirapex for $D_3$ receptors is 7–10 times greater than that for $D_2$ receptors [11, 23, 35, 46]. Interactions with $\alpha$-adrenoreceptors and serotonin receptors are minimal. Extensive preclinical studies led to the hypothesis that low

TABLE 2. Dopamine Receptor Agonists

| DRA | Commercial name | Content of active substance in tablets, mg | Daily dose, mg |
|---|---|---|---|
| *Ergoline* | | | |
| Bromocriptine | Parlodel | 2.5 | 10–40 |
| | Bromocriptin | 2.5; 5; 10 | |
| Lisuride | Lisenil | 0.2 | 0.4–6.0 |
| Pergolide | Permax | 0.05; 0.25; 1.0 | 0.75–5.0 |
| Cabergoline | Dostinex | 0.5 | 1.5–5.0 |
| | Cabsar | 0.5 | |
| *Non-ergoline* | | | |
| Pramipexole | Mirapex | 0.125; 0.25; 1.0 | 1.5–4.5 |
| Piribedil | Trivastal | 25; 50 | 100–250 |
| | Pronoran | 50 | |
| Ropinirol | Requip | 0.25 | 1.5–2.4 |

TABLE 3. Pharmacokinetic Properties of DRA

| Agent | Bioavailability, % | Metabolism, excretion | Halflife, h |
|---|---|---|---|
| Mirapex | 90 | Excretion via kidneys | 8–12 |
| Piribedil | 90 | Ditto | 2–7 |
| Bromocriptine | 8 | Metabolized in the liver | 3–8 |
| Pergolide | 20 | Ditto | 15–27 |
| Ropinirol | 55 | » | 6 |

doses of Mirapex act on $D_2/D_3$ presynaptic autoreceptors, resulting in dopamine release, while high doses activate postsynaptic $D_2/D_3$ receptors. Given that the function of presynaptic receptors is decreased in PD as a result of neuron degeneration, the main mechanism of action of Mirapex in PD is its interaction with postsynaptic receptors [32].

Mirapex is absorbed rapidly after oral dosage, has high bioavailability (greater than 90%), and is excreted via the kidneys (90%). Hepatic metabolism is minimal and there is virtually no interaction with cytochrome, an enzyme which alters interactions with other therapeutic agents.

Mirapex shows a linear dose-response relationship; its plasma halflife in healthy subjects is 8 h, compared with 12 h in subjects aged more than 65 years (see Table 3). Clinical studies have demonstrated that the increased plasma halflife in the elderly does not increase the risk of side effects.

*Clinical efficacy of Mirapex.* The efficacy of Mirapex has been established in many double-blind, placebo-controlled studies in both the early and late stages of PD [2, 17, 18, 20, 22, 26, 33, 36, 48, 51, 52, 55]. Monotherapy in the early stages of the disease leads to increases in the daily activity of patients and improvements in motor functions; in the late stages there are reductions in motor fluctuations and dyskinesias. Thus, use of Mirapex at a dose of 3.8 mg/day in the early stages PD yielded significant decreases (by 25%) in the severity of motor symptoms and 22% increases in daily activity (UPDRS scale) as compared with baseline. Many patients can remain on Mirapex monotherapy for more than three years with satisfactory daily activity before the need for levodopa preparations arises [38].

Comparative studies [48] have shown that Mirapex at a dose of 4.5 mg/day is more effective than bromocriptine at a dose of 20–30 mg/day in the late stage of PD. Other studies [17, 30, 52] have shown that treatment with Mirapex at the initial stages of treatment significantly delays the appearance of the first motor fluctuations and therapeutic dyskinesias. In addition, a double-blind, placebo-controlled study of the efficacy of Mirapex (4.5 mg/day) in the late stages of PD demonstrated a significant improvement in measures of motor activity and daily activity, with a 31% decrease in the off period, an increase in the on period by 2 h per day, and a 24% reduction in the severity of therapeutic dyskinesias. There was also a significant reduction in the daily dose of levodopa (by 27%), which also allowed, without any loss in the efficacy of pharmacotherapy, reductions in the peak-dose therapeutic dyskinesias.

*Effects of Mirapex on depression.* Depression is known to occur in 40–70% of cases of PD. Depression significantly degrades the quality of life and daily activity, decreases the efficacy of treatment, aggravates the course of disease, and is also a risk factor for the development of cognitive impairments in the late stages of the disease [12]. Dopamine receptor agonists have been shown to have therapeutic effects on depression [39, 53], with the result that they have been studied in relation to PD-associated depression.

The selective stimulation of $D_3$ receptors in the limbic system by Mirapex allows it to produce a general reduction in the severity of depressive syndrome. Thus, a double-blind, placebo-controlled study with the purpose of assessing the efficacy of Mirapex in the treatment of major depression in mental patients without PD [12] showed that the group of patients receiving Mirapex for eight weeks at a daily dose of 5 mg showed a significant decrease in the depth of depression (on the Hamilton scale). Its efficacy was greater than that of fluoxetine (20 mg/day). In other studies [43, 49], the combination of levodopa and Mirapex produced significant regression of depression in patients with PD after treatment for 2–3 months.

*Effects of Mirapex on tremor.* Tremor is seen in 70–75% of patients with PD [34]. A double-blind, placebo-controlled trial [22] compared the effects of levodopa alone and with Mirapex on tremor in patients with PD. Addition of Mirapex to levodopa yielded a more marked regression of tremor – by 65%, compared with 35% in patients treated with levodopa alone.

*Dose regime.* Most DRA are given three times daily, the exception being cabergoline, which has a long elimination halflife (48–65 h) and it used once daily. At the start of DRA therapy, when the dose is being titrated, there is sometimes a slight and transient increase in the severity of PD symptoms associated with activation of presynaptic autoreceptors and enhanced dopamine reuptake.

The daily dose of DRA, as for most other antiparkinsonism agents, is selected gradually, over a period of 3–5 weeks, by titration, with doses increasing slowly until the therapeutic effect is obtained, when the dose is stabilized.

Therapeutic doses of Mirapex are determined as follows: the dose during the first week of treatment is 0.125 mg t.i.d., increasing to 0.250 mg t.i.d. during the second week, 0.5 mg t.i.d. during the third week, 1 mg t.i.d. during the fourth week, and so on until an effective therapeutic dose is identified. The maximum dose is 4.5 mg/day.

The results of clinical trials, including our study, have provided evidence that the efficacy of the treatment of PD can be increased by substituting one DRA with another. Transfer to treatment with other DRA can be achieved in two ways: by gradual sequential decreases in the dose of the agent being used with slow increases in the dose of the new agent, or by sudden withdrawal of the agent being used and initiation of treatment with an equivalent dose of the new DRA the morning following the evening dose of the agent being used.

The safety and efficacy of rapid transfer from various DRA to Mirapex were assessed in the later stages of PD in an open multicenter trial [23] involving 227 patients treated with levodopa preparations in combination with a DRA (bromocriptine, pergolide, or ropinirol). Patients were immediately transferred to Mirapex at the following dose ratios: 1 mg of Mirapex for 1 mg pergolide, 10 mg of bromocriptine, or 4 mg of ropinirol. The results demonstrated significant improvements in motor functions and successful correction of motor fluctuations. In other words, it was shown that rapid substitution of DRA is safe, which allows deterioration in the state of patients with PD during gradual withdrawal of the previous treatment with slow increases in daily dose of the new DRA to be avoided.

*Neuroprotective effects of DCS.* This effect of new-generation agents (Mirapex, ropinirol) is associated with a decrease in the synaptic metabolism of dopamine, stimulation of $D_1$ receptors, the synthesis of proteins with antioxidant properties, stimulation of autotrophic neuron activity, decreases in the PD tone of disinhibitory brain structures (the subthalamic nuclei), and decreases in glutamate release [28, 45, 50].

The neuroprotective effect of Mirapex has been demonstrated in experimental studies [7]: it has a protective effect, preventing the toxic effect of levodopa in embryonic mesenchymal neuron cultures and decreasing dopamine loss in toxic parkinsonism in experimental animals. In addition, its antioxidant properties give rise to decreases in the quantity of free radicals in experimental lesions to strionigral neurons and increases in cell survival in ischemic brain damage [10].

Investigations presented by the PD Study Group using sequential SPECT (single-photon emission CT) scanning [32] with the radiopharmaceutical agent β-CIT showed that loss of dopamine transporters at two years of observations was 20% lower in a group of patients initially treated with Mirapex than in those given levodopa (by 25%). Although differences in this initial short-term study were not statistically significant, it was suggested that longer-term observations would demonstrate a positive effect of Mirapex in relation to delaying the rate of progression of PD.

*Side effects of Mirapex.* Many studies have indicated that Mirapex is well tolerated. The level of stimulation of non-dopamine receptors (α-adrenoreceptors, serotonin receptors, muscarinic receptors) with Mirapex is lower than with bromocriptine; the incidence of peripheral autonomic, cardiovascular, and gastroenterological side effects is lower. The non-ergoline nature of this agents also excludes such complications as gastric ulcers, peripheral vasospasm, and pulmonary and retroperitoneal fibrosis. Daytime drowsiness, hallucinations, and gastroenterological symptoms are seen somewhat more frequently than with the use of DCS. Attention is drawn to the fact that side effects are more often seen during the titration period of the (increasing)

TABLE 4. Extent of Major Symptoms on the UPDRS Before and After Treatment with Mirapex, points ($M \pm m$)

| Symptom | Before treatment | After treatment | % improvement |
|---|---|---|---|
| Tremor | 9.4 ± 3.5 | 6.6 ± 2.9* | 29 |
| Rigidity | 10.7 ± 2.1 | 7.6 ± 1.6* | 28 |
| Hypokinesia | 1.2 ± 0.6 | 0.5 ± 0.5* | 58 |
| Postural instability | 1.1 ± 0.5 | 0.7 ± 0.4 | 37 |

**Note.** *$p < 0.01$.

Mirapex dose, especially in the early stages of PD (the cause of this phenomenon remains unclear) [47, 51, 55].

Summarizing these published data, new-generation DRA have advantages in comparison with levodopa agents: direct stimulation of dopamine receptors, the absence of metabolic transformations; the absence of competition with dietary amino acids for intestinal absorption and penetration through the blood-brain barrier; the halflife, which gives a stable and near-physiological stimulation of dopamine receptors, which decreases the risk of developing motor fluctuations and therapeutic dyskinesias; the absence of oxidative metabolism of DRA with the resultant non-production of free hydroxyl radicals able to degrade molecules containing DNA, proteins, and membrane lipids and to accelerate neuron apoptosis; the potential neuroprotective effect.

### Data from our Own Studies

Our studies were designed to assess the pharmacotherapeutic efficacy of Mirapex as a supplementary therapy in the treatment of patients in the late stages of PD. The aims were to analyze its efficacy in the treatment of motor disorders in the late stages of PD, in the correction of motor fluctuations and therapeutic dyskinesias in conditions of prolonged treatment with DCS, and to assess the influence of Mirapex on the daily activity and quality of life of patients with PD and on cognitive and affective impairments in this disease.

## MATERIALS AND METHODS

A total of 30 patients – 16 men and 14 women – in the late stage of PD were treated with Mirapex. The mean age at disease onset was 61.8 ± 7.7. years and disease duration was 8.4 ± 1.3 years; disease severity on the Hoehn and Yahr scale was 2.6 ± 0.4 points (at the peak effect of a single dose of DCS).

All patients received levodopa agents (Nakom or Madopar) at a dose of 667.8 ± 166.4 mg/day. The duration of this treatment at the start of the study averaged 7 ± 1.2 years.

Mirapex doses were determined by titration with a gradual increase in dose from 0.375 to 4.5 mg/day, with a mean daily dose of 3.5 ± 1.1 mg/day.

The efficacy of pharmacotherapy was assessed using a number of scales. The severity of motor impairments was assessed on the Unified Parkinson's Disease Rating Scale (UPDRS), the Tinetti Balance and Motor Activity Scale, and the Schwab and England Daily Activity Scale.

The extent of the single DCS dose depletion phenomenon was analyzed in terms of the dynamics of the duration of action of a single DCS dose using patients' self-evaluation diaries.

The extent of therapeutic dyskinesias was assessed using the Obeso scale and the UPDRS (part IV). The duration of the daytime on period (the better state of motor activity) was assessed using the original coefficient of efficacy (CE) consisting of the percentage of time spent in the best state (on) to the total during of waking (on + off):

$$CE = (on)/(on + off) \times 100\%.$$

Cognitive impairments were assessed using the MMSE and Mattis scales; depression and anxiety were evaluated on the Hamilton scale. Quality of life was assessed using the PDQ-39 questionnaire.

Safety during the clinical observations (before and after treatment) was evaluated using electrocardiography and laboratory tests (general tests, blood biochemistry, urinalysis).

Data were analyzed statistically using Statistica 4.3 for Windows. Non-parametric data analysis methods were used – the signs test, the Wilcoxon test, and the Spearman correlation coefficient.

## RESULTS AND DISCUSSION

Treatment with Mirapex was followed by an improvement in the patients' state on the UPDRS and Hoehn and Yahr scales; points on the former changed from 71.1 ± 14.9 to 60.1 ± 14.2 and points on the latter changed from 2.9 ± 0.4 to 2.6 ± 0.4, i.e., there was a 16% improvement on the UPDRS and a 10.3% decrease in severity on the Hoehn and Yahr scale (significant difference, $p < 0.01$). There were also significant improvements in motor activity, daily activity, and quality of life.

Motor activity increased by 13%, from 26.9 ± 6.1% to 30.4 ± 5.8% ($p < 0.01$). This was accompanied by regres-

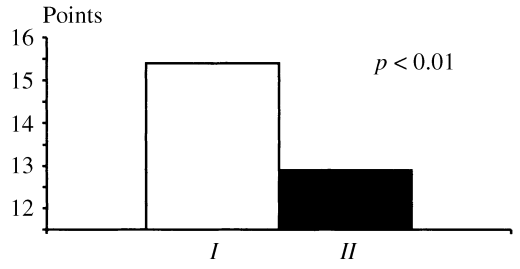


Fig. 1. Daily activity of patients on UPDRS (part II) before (*I*) and after (*II*) treatment with Mirapex.

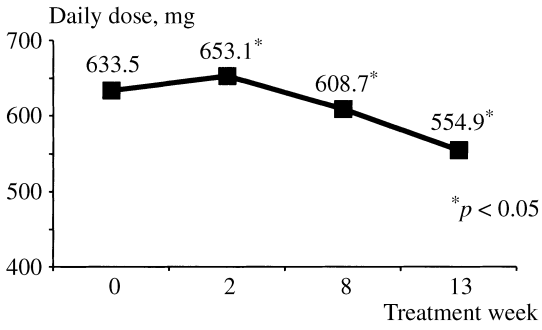


Fig. 2. Changes in daily levodopa dose after treatment with Mirapex.

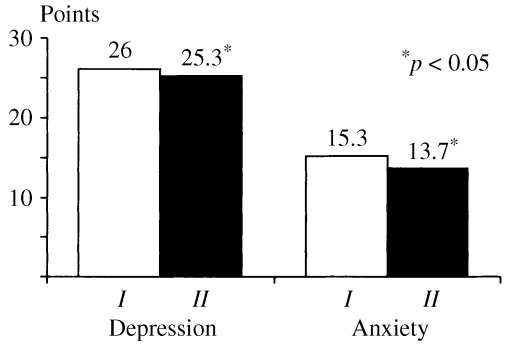


Fig. 3. Extent of emotional disorders before (*I*) and after (*II*) treatment with Mirapex.

sion of PD symptoms such as tremor, rigidity, hypokinesia, and postural instability.

The corresponding data are shown in Table. 4.

There were significant reductions in hypokinesia (by 58%), tremor (by 29%), and rigidity (by 28%). Figure 1 shows changes in patients' daily activity on the UPDRS, i.e., a 16% increase. As regards quality of life, this improved by 20%, from 82.4 ± 13.3 to 98.1 ± 12.7 points ($p < 0.01$).

It has already been noted that most patients in the late stages of PD have motor fluctuations and therapeutic dyskinesias. Thus, we addressed the possibility of decreasing the DCS dose with the aim of correcting peak-dose therapeutic dyskinesias. Analysis of the results showed that from treatment week 8 the levodopa dose could be decreased by 13% without any reduction in motor activity (Fig. 2). Mirapex treatment was followed by a decrease in the severity of dyskinesias, by 33% on the UPDRS (from 11.5 ± 5.8 to 7.7 ± 5.1 points; $p < 0.01$) and by 19% on the Obeso scale (from 2.1 ± 0.7 to 1.8 ± 0.6 points, $p < 0.01$). In addition, Mirapex allowed a significant increase in the duration of action of single DCS doses (the on period), by 17%; there was a significant reduction in the severity of freezing associated with use of Mirapex – by 30% compared with baseline (Table 5).

Mirapex also allowed a significant regression of anxiety and depression (Fig. 3), with improvements in logical (by 34%) and visual (by 20%) memory. In addition, there was a significant (30%) increase in speech activity in directed association tests, with a significant increase (by 11%) in verbal activity (Table 6).

The pattern of side effects was dominated by gastroenterological symptoms (19% of cases). Drowsiness was less frequent, occurring in 3% of patients.

The combined data from the literature and our own studies can be interpreted as follows.

Preclinical studies showed that Mirapex decreases motor impairments in toxic parkinsonism in experimental animals, has a neuroprotective action, including in patients with PD, and is characterized by high efficacy and safety in the treatment of both early and later stages of PD.

Our own results support the high efficacy of Mirapex in combination with DCS in the late stages of PD, with significant decreases in the severity of the major clinical symptoms and increases in daily activity and measures of the patients' quality of life. A significant aspect of the action of Mirapex is the decrease in the severity of motor fluctuations and therapeutic dyskinesias. In addition, Mirapex had positive influences on the emotional sphere and the patients' cognitive functions. Mirapex allowed decreases in the daily levodopa dose.

Thus, clinical application of DRA facilitated a significant improvement in the pharmacotherapeutic strategy for the treatment of PD.

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TABLE 5. Duration of Daytime On Period and Extent of Freezing Before and After Treatment with Mirapex

| Measure | Before treatment | After treatment | $p$ |
|---|---|---|---|
| Duration of daytime on period, *t*/% | 62.4 | 71.2* | <0.01 |
| Extent of freezing, points | 56.6 | 27** | <0.05 |

TABLE 6. Neuropsychological Tests in Patients with PD Before and After Treatment with Mirapex, points ($M \pm m$, $p < 0.01$)

| Neuropsychological function | Before treatment | After treatment |
|---|---|---|
| Memory: | | |
| logical | 7.5 ± 4.8 | 10.1 ± 2.6 |
| visual | 7.4 ± 2.3 | 8.9 ± 1.9 |
| Speech: | | |
| verbal activity (words) | 23.4 ± 10.5 | 26.0 ± 8.3 |
| words beginning with *l* | 10.8 ± 3.2 | 14.1 ± 1.0 |
| Semantic index | 2.1 ± 0.9 | 3.1 ± 9.2 |


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