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Parkinson's Disease – Challenges in New Drug Development

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A B S T R A C T

Idiopathic Parkinson's disease (IPD) is the second most common neurodegenerative disorder after Alzheimer's disease. Treatment aims in IPD include the provision of symptomatic relief, reduction of functional disability, halting or slowing of the neurodegenerative process, and the prevention of long-term complications by proper initiation of therapy. At present, pharmacotherapeutic strategies allow the amelioration of motor symptoms of IPD only, whereas non-motor manifestations are not helped by dopamine replacement strategies. In addition, levodopa-induced fluctuation and dyskinesia are still challenging, particularly in long-term treatment. Despite advances in pharmacotherapy that have improved quality of life for these patients, the mortality rate remains largely unchanged. Sustained interest in IPD will hopefully allow increased funding of research to develop new and better treatments.

Key words: *Parkinson's disease, therapy, levodopa, dopamine agonists*

Introduction

Idiopathic Parkinson's disease (IPD) is the second most common neurodegenerative disorder after Alzheimer's disease, with over 100,000 patients diagnosed in the United Kingdom and at least 8,000 new cases diagnosed annually. In the United States, approximately 1% of those over 65 and 3% of those over 85 years of age are diagnosed with IPD[1]. Prevalence and incidence will continue to increase with the aging population. IPD is characterized pathologically by the loss of pigmented dopaminergic neurons associated with eosinophilic cytoplasmatic inclusions (Lewy body) mainly in the substantia nigra and locus ceruleus. This neuronal loss results in a significant decrease of dopamine levels in the brain; patients become symptomatic when this decrease is over a certain threshold. The course of the clinical decline parallels that of the progressive degeneration of the remaining dopaminergic neurons[2].

Although IPD is relatively common, it can be difficult to diagnose clinically, particularly in early stages. Approximately 5 to 10% of patients with IPD are misdiagnosed[3]. Conversely, up to 20% of patients diagnosed with IPD reveal alternative diagnoses at autopsy, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Alzheimer's disease type pathology, and cerebrovascular disease[4–7]. Diagnostic criteria such as the UK PD Society Brain Bank criteria[3] have been developed; however, it has been suggested that an accuracy of 90% is the best that can be achieved with clinical assessment and clinical diagnostic criteria[5].

Clinical Presentation

The UK PD Society Brain Bank criteria allows for differentiation between IPD and parkinsonism. The term parkinsonism refers to a clinical syndrome comprising combinations of motor symptoms and signs: bradykinesia (slowness and decreased amplitude of movement), tremor-at-rest, muscle rigidity, loss of postural reflexes, flexed posture, and the freezing phenomenon (where the feet are transiently »glued« to the ground). At least two of these six cardinal features need to be present before the diagnosis of parkinsonism is made, with at least one of them being tremor-at-rest or bradykinesia. Idiopathic Parkinson disease is the major cause of parkinsonism and can also be referred to as primary parkinsonism, in contrast to the other three parkinsonian designations, namely: 1) secondary, such as drug-induced parkinsonism,

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postencephalitic, vascular, mass-lesion induced, or toxic parkinsonism; 2) Parkinson-plus syndromes (presence of parkinsonism plus other neurological features) such as progressive supranuclear palsy (PSP), multisystem atrophy (MSA), corticobasal degeneration (CBD); and 3) herodegenerative disorders in which parkinsonism is only one feature of a hereditary degenerative disorder, such as juvenile Huntington's disease and Wilson's disease. Three of the most helpful indicators of IPD that distinguish it from another category of parkinsonism are: 1) an asymmetrical onset of symptoms and signs (IPD often begins on one side of the body), 2) the presence of resting tremor (although resting tremor may be absent in patients with IPD – it is almost always absent in Parkinson plus syndromes), and 3) substantial clinical response to adequate levodopa therapy (usually Parkinson-plus syndromes do not respond to levodopa therapy)[8]. IPD is a slowly progressive parkinsonian syndrome that begins insidiously, gradually worsens in severity, and usually affects one side of the body before spreading to involve the other side. Resting tremor is often the first symptom recognized by the patient, but the illness sometimes begins with bradykinesia. In some patients, tremor may never develop. Symptoms steadily worsen over time, which, if untreated, leads to disability with severe immobility and increased risk of falling. The early symptoms and signs of IPD (rest tremor, bradykinesia, and rigidity) are usually correctable by treatment with levodopa or/and dopamine (DA) agonists. As IPD progresses over time, symptoms that respond poorly to levodopa or DA agonists develop, such as flexed posture, the freezing phenomenon, and loss of postural reflexes; these are often referred to as non-DA-related features of PD. Moreover, bradykinesia that responded to levodopa or DA agonists in the early stage of IPD increases as the disease worsens and no longer fully responds to levodopa or DA agonists. It is particularly these intractable motor symptoms that lead to the progressive disability. Disability associated with IPD includes not only motor dysfunction, but also many non-motor symptoms like dysautonomia (autonomic nervous system dysfunction), fatigue, depression, anxiety, sleep disturbances, constipation, bladder and other autonomic disturbances (sexual, gastrointestinal), sensory complaints, decreased motivation and apathy, slowness in thinking (bradyphrenia), and a declining cognition that can progress to dementia.

Challenges of the Current Treatment Strategy

Currently available therapies are most effective in minimizing the motor dysfunction of IPD through increasing the activity of the remaining intact neurons (not affected, or only partially affected by degeneration) of the nigrostriatal dopamine system. Nearly 70–80% of dopaminergic neurons have already degenerated when first signs of disease have become evident[2]. Since only 20–30% of remaining dopaminergic neurons are available to the current pharmacological intervention and the degenerative process continues, it is clear why the overall benefit of treatment is partial and not sustained over the years of disease. In the early stages of the disease, the brain still retains sufficient dopaminergic reserves to buffer the fluctuations in dopaminergic stimulation by the exogenous dopaminergic medications[9]; despite levodopa having a short half-life (60 to 90 minutes)[10], patients still experience benefit despite missing a dose of medication[11]. As dopaminergic neurons continue to degenerate in this progressive disease, the fluctuations manifest clinically as the buffering capacity diminishes[9] and the striatum becomes dependent on the peripheral availability of levodopa[12]. This leads to motor fluctuations, where the patient alternates between »on« periods in which levodopa provides benefit, and »off« periods when the levodopa benefit »wears off« prior to the next dose with worsening symptoms[11]. These unbuffered fluctuations in the plasma concentration of short-acting levodopa may impact directly on the striatum, with alternating high and low levels of striatal dopamine exposed to dopamine receptors. This pulsatile stimulation of the striatal dopamine receptors is now thought to be a key factor in the development of the levodopa-associated motor complications of IPD[11] through induction of changes in striatal neuronal plasticity, dysregulation of genes and proteins, and alterations in neuronal firing patterns[12]. Observations that the half-life of dopaminergic agents and disease severity (i.e., degree of nigrostriatal cell loss) are important factors in the development of motor fluctuations and dyskinesias[13] are consistent with this hypothesis. These motor complications can impair quality of life and cause significant disability[14]. Risk factors for motor complications include younger age at onset of IPD, disease severity, higher levodopa dosage, and longer disease duration and levodopa treatment[15–16]. Several types of motor fluctuations have been described, the most common being the »wearing-off« effect. With this pattern, patients develop a predictable worsening of their parkinsonism at the end of their current dose and before their next scheduled dose of levodopa. This leaves them in an »off« state, in which clinical features such as tremor, bradykinesia, and limb rigidity return. Off state symptoms can be disabling because they lead to immobility. Some patients react to off states with panic attacks, screaming, or even drenching sweats[17]. The predictability of these off states enables the patients to clearly describe the average length of their »on« states and the duration and number of off states during the day. A predictable wearing off effect might be expected in nearly 20% of patients treated with levodopa within 5 years, 45% treated within 9 years, and 100% of those treated more than 10 years[16]. The pathophysiology of the wearing-off effect is believed to relate to disease progression and the pharmacokinetics of levodopa. As the disease progresses, the duration of the on state progressively shortens, presumably owing to the reduced capacity for presynaptic storage of dopamine by nigral neurons[18]. Due to levodopa's short half-life, the duration of the typical on state progressively shortens as the disease progresses until the on states may last no longer than 1 hour. With disease

progression, there is a tendency for the fluctuations to become increasingly less predictable. As the wearing off becomes more complicated, dosing responses also vary and patients may report a »delayedon« effect or dose failures (otherwise known as the »no-on« effect or the »skipped-dose« effect). Delayed-on refers to a significant and unusual delay between the taking of a dose of levodopa and the commencement of its effects. No-on occurs when a given dose of levodopa is not effective at all. When this happens, the off state is dramatically prolonged, further increasing disability. The timing of these events is often unpredictable. In many patients, it seems that the majority of the total daily off time is actually time spent waiting for a dose of levodopa to take effect[19]. The on–off effect is the most unpredictable of fluctuating states. This also produces off states, but in a seemingly random fashion, such that patients cannot predict when the next off state will occur. These episodes vary in time, are unrelated to medication doses, and occur suddenly. Patients with the on-off effect usually have more advanced disease. This phenomenon is rarely seen within the first 5 years of levodopa treatment, but it is present in 50% of those treated more than 10 years[16]. Most patients with the on-off effect also experience the wearing off effect, so that some off states may be predictable and others are not. The unpredictability of off states significantly increases disability and negatively affects patient quality of life. The underlying cause of the on-off effect is poorly understood. The pharmacokinetic and pharmacodynamic proprieties of levodopa have been considered as possible explanation of this phenomenon, but it is still a mystery why the effect occurs only in very advanced IPD. In addition to levodopa-related periods of immobility, many patients experience levodopa-induced dyskinesias. Unlike the off phenomenon, dyskinesias usually accompany the on state. The most common type of dyskinesia is seen at the peak of the clinical effect of levodopa, so-called »peak-dose« dyskinesias. It is rare within the first 5 years of levodopa treatment (11%), but very common after 10 years of treatment (89%)[16]. These movements (which are typically choreiform or dystonic) can be mild and of no consequence, or severe enough to be disabling. The chief importance of dyskinesias when the treatment of off states is considered is the fact that most medical strategies for reducing off states have increased dyskinesias as a side effect. It is often necessary to strike a balance between minimizing off time while not greatly accentuating dyskinesias. Another form of dyskinesia is diphasic dyskinesia, where choreic or dystonic movements occur at the beginning or end of the levodopa dose as the serum levels are changing. It appears to involve legs more than the other types of dyskinesia, and it also appears to be more troublesome than the peak-dose type. Some patients have both types and therefore experience dyskinesias during the entire on state. The current concept of pharmacological treatment in early IPD is purely symptomatic and directed to the motor symptoms only. It should be considered for the patient who develops functional disability, which varies with the individual. Patients with no functional disability may be prescribed non-pharmacological measures like exercise, educational programs, and support services with close monitoring of symptoms and quality of life. Once symptomatic treatment is needed, the minimal dose of medication that reverses the disability should be used[20]. Levodopa is the most effective antiparkinsonian agent[12]. As such, any medication to increase its bioavailability and elimination half-life (COMT inhibitors, MAO-B inhibitors, dopamine reuptake inhibitors) would allow for less pulsatile dopaminergic stimulation. However, DA agonists are preferred as first-line agents[11], particularly in patients with a young onset of IPD. There are several reasons for such an approach. Studies of non-ergot DA agonists alone in early IPD showed successful treatment for several years[21], although these studies did not confirm non-inferiority to levodopa. Moreover, long term head-to-head studies with levodopa found a delay in time to onset of motor complications with DA agonists[21], but at the expense of poorer control of the symptoms of Parkinson's disease and an increase in psychiatric complications such as hallucinations – which may be more important for patients and caregivers than motor complications. DA agonists have emerged as neuroprotective candidates, based on laboratory studies demonstrating their ability to protect dopaminergic and non-dopaminergic neurons in both in vitro and in vivo models[22] and clinical evidence based on CALM-PD[23] and REAL-PET[24] studies. DA agonists in clinical use also have longer half-lives than levodopa and may have a longer duration of symptomatic effect. Additionally, levodopa has been shown to be neurotoxic in vitro experiments although this neurotoxicity has not been shown in vivo[25] and are associated with sudden irresistible sleep attacks[26], excessive daytime sleepiness[27], cognitive impairment, and psychosis[11]. Conversely, fibrotic pericardial and valvular heart disease and pulmonary and retroperitoneal fibrosis have been reported with ergot-derived DA agonists[28–30], but not yet with non-ergot DA agonists (ropinirole, pramipexole rotigotine). In young patients, because of the longer treatment horizon, it is preferable to initiate therapy with a non-ergot DA such as rotigotine, pramipexole or ropinirole. Older patients are usually commenced on levodopa therapy, because they have a shorter treatment horizon, are more liable to develop cognitive and psychiatric complications, and are thought to be less likely to develop motor fluctuations and dyskinesias with levodopa. Regardless of initial selection of antiparkinsonian drug, L-dopa will be eventually used and will inevitably induce motor complications during long-term treatment.

Further Directions of Development

Despite the number of agents approved for use in IPD, neither a risk-free treatment with sustained benefit nor has a preventive or curative agent been identified. In addition, little is known regarding the benefit of any therapeutic agent for a period of more than a few years. A review of all trials so far found that the median follow-up period per trial was two years; only 40% of trials

in early PD went beyond 12 months. Therefore, there is a need for new drug development in all aspects of PD therapy. Development of a treatment with sustained therapeutic benefit over the decades of the disease would be invaluable. The current concept of drug development in IPD is directed to neuroprotection including slowing disease progression, motor symptoms and signs, complications induced by long-term L-dopa treatment, and non-motor symptoms and signs following IPD.

Neuroprotection strategy

Ideally, neuroprotective drugs should be considered as pharmaco-prophylactic approach in the high risk population, before clinically manifesting disease. However, neither such population nor agents have been identified so far. Much effort has been directed to the development of treatments that can stop or slow the progression of established disease, but such an agent has not been identified unequivocally. There is no uniform opinion with regard to the planning and conduct of such studies. Since there is no biomarker of Parkinson's disease progression, primary endpoints are based on clinical measures of parkinsonism. Because most people with Parkinson's disease require symptomatic therapy within several months to one year of diagnosis, such studies typically enroll only those early in the course of disease who do not require symptomatic therapy. New techniques are in development for measuring cerebral dopamine uptake and dopamine receptor density (SPECT and PET). The value of diminished cerebral dopamine uptake and dopamine receptor density for measuring neuroprotective effect remains to be established, as the predictive value of these variables for the rate of progression in IPD has not been validated. A method widely used in order to distinguish a symptomatic effect from a neuroprotective effect is to demonstrate that the effect is maintained in the active treatment group relative to placebo after sufficient washout of the study drug at the end of the treatment period. A neuroprotective effect would be maintained whereas a symptomatic effect would not be maintained. Care should be taken to avoid confounding these effects with changes in other symptomatic treatments and to avoid carry-over effects due to unstable dopamine receptor sensitivity. A typical development plan to investigate a drug proposed to slow the progression of parkinsonism will include several multicenter, double-blind, placebo controlled trials investigating the safety and efficacy of one or several doses of the drug. Patients included are recently diagnosed and not in need of symptomatic therapy. Prior exposure to symptomatic antiparkinsonian therapy is precluded, or limited to a short time. Other agents proposed to slow the progression of parkinsonism are also excluded. Primary endpoints trials designed to evaluate a delay in progression of parkinsonism may include a need to start dopaminergic therapy or a prespecified increase in a standard measurement tool of parkinsonism. Secondary endpoints may include Unified Parkinson's Disease Rating Scale (UPDRS) scores, Hoehn and Yahr stage of illness, Schwab and England rating scale score, and Clinical Global Impressions of Severity and Change, as well as disease-specific Quality of Life measures (e.g., the PDQ-39, and PDQUALIF) or generic Quality of Life measures (e.g., the EuroQol and SF-36) at specified time points. Exploratory endpoints depend on the chemistry of the intervention and can include non-motor elements of Parkinson's disease such as depression, cognition, hallucinations, and dysautonomia. Rating scales for all of these are derived from standard scales in the medical literature and have not been developed specifically for Parkinson's disease in most instances. A new form of the UPDRS has been recently developed[31] as has a non-motor symptom assessment scale for Parkinson's disease[32], but these have not yet been validated in clinical practice. Because a neuroprotective drug would be expected to be used for many years, or even for the entire duration of disease, safety monitoring should allow detection of events expected to occur at moderate frequency (0.5–5%). In general, around 1200–1500 persons exposed in short- and long-term studies should be adequate to detect differences of around 2 to 3% across groups. To detect adverse events occurring after prolonged use of the drug, duration of monitoring should be at least 12 months for some subjects. Depending on the specific agent, special safety monitoring may be indicated.

Development of drugs for symptomatic treatment of motor symptoms

While there are a number of agents with demonstrated antiparkinsonian efficacy, none provides sustained symptomatic benefit throughout the course of this disorder. The acute and chronic side effects of established therapies are additional sources of concern. Trials of new therapies should be designed to address these concerns, with the goal of developing new drugs with more favorable efficacy and side effect profiles. A typical development plan to investigate a drug proposed to provide symptomatic improvement of parkinsonism would include several multicenter, double-blind, placebo-controlled trials investigating the safety and efficacy of one or several doses of the drug. Monotherapy trials, comparing the study drug to placebo, will in most cases be limited to early disease, enrolling »de novo« patients receiving symptomatic therapy for the first time. Early monotherapy studies restrict subjects to Hoehn-Yahr stage I–III (unilateral or bilateral disease that may include mild balance problems but no spontaneous falling) and sometimes to Stage I–II only (no balance problems). The UPDRS is often used as the primary endpoint and may include the Total score, part III only (examination of motor function), or part III + part II (patient's motor activity of daily living). Secondary and exploratory endpoints are similar to those described in the neuroprotection strategy. Because there is inevitable subjectivity in endpoint determination, it is almost always desirable to require that the primary outcome measure be determined by the same rater, at a minimum for key time points (such as enrollment and endpoint). It may be desirable to identify specific raters within a center and/or to specify a re-

quired level of expertise with the primary efficacy measure. A blocked randomization, either by investigator or by center, is another approach to minimize the effect of between-rater variability. To avoid »unblinding« and the potential for a biased endpoint assessment, two raters may be used – a »treating« investigator who evaluates the patient at each visit and a »blinded« investigator who determines performance on primary outcome measures only at key visits and is otherwise prohibited from knowledge of the subject. Follow-up is often continued after primary efficacy data have been obtained, whereas an extended follow-up can be especially valuable in monitoring safety and to assess chronic efficacy. The analysis of efficacy variables is based on the intention-to-treat strategy. All statistical tests are two sided, and p-values <0.05 are considered statistically significant, though sometimes adjusted p-values are used to account for multiple comparisons. In studies of advanced Parkinson's disease, the study drug will typically be given as adjunctive therapy and compared to placebo given adjunctively, as it would be unethical to withdraw existing therapies. Most commonly, the efficacy of the new agent when given in combination with a dopaminergic agent (usually L-dopa plus decarboxylase inhibitor) is compared to the efficacy of placebo combined with the same agent. Studies of drugs that are added to current treatment in moderate Parkinson's disease usually restrict patients to Hoehn-Yahr stage II–IV and therefore include patients with poor balance. The addition of an adjunctive antiparkinsonian agent can result not only in improvement of parkinsonism, but also in the new onset of dopaminergic side effects or the worsening of existing side effects, such as dyskinesias or psychosis. Therefore, primary outcome measures may include the UPDRS (total or Part III, or Parts II + III for parkinsonism), the Abnormal Involuntary Movement Scale (AIMS), the Rush Dyskinesia Scale in conjunction with a patient home diary for dyskinesia, and the UPDRS part III/IV in conjunction with a patient home diary for motor fluctuations. In addition, a global measure such as a disease-specific quality of life measure is essential, as it is otherwise impossible to interpret an improvement in motor function coupled with a deterioration in side effects. An alternative design compares the new drug to standard therapy. Design of such studies is often difficult due to uncertainty regarding equivalence of dosage. Some regulatory agencies may be less receptive to comparison study designs. As for all development plans, close contact with scientists in the regulatory agencies is essential. Safety evaluations should take into account the chronic use expected for most drugs in this category. Therefore, safety monitoring should allow detection of events expected to occur at moderate frequency.

Development of drugs for the improvement of already existing dyskinesia and motor fluctuations

Dyskinesia and motor fluctuations are inevitable side effects for most patients requiring L-dopa. These side effects are less frequently associated with DA agonists. Studies focused to improve existing dyskinesias or motor fluctuations are highly dependant on patient record and require additional training of both investigators and patients. Patients have to be trained to recognize motor fluctuation, make a difference between sensory and motor symptoms in various periods of L-dopa response, and eventually properly record all those changes for trial purposes. Dyskinesia are often intermittent, lasting from several minutes to few hours, and very often patients are not able to identify mild or even moderate dyskinesia. Assessment of dyskinesia includes assessment of both its severity and duration. Severity of dyskinesia is usually rated with various scales like the AIMS or Rush dyskinesia scale, assessing all limbs, trunk, face, and neck, but very often due to intermittent nature of movement disorder, results can be inappropriate or misinterpreted. In addition, dyskinesia can be activated by motor or mental tasks, giving an incorrect impression of its severity. For studies of motor fluctuations and dyskinesia, inclusion criteria usually require baseline scores for the target problem sufficiently severe enough to allow for deterioration during the trial. For dyskinesias, a minimal baseline severity score on the AIMS (variably 7–10) is often used, together with minimal daily duration of dyskinesia between 26–50% based on diaries or UPDRS. For motor fluctuation, inclusion often requires a minimal 2 to 3 hours daily of off time recorded in the patient's diary between screening and baseline visits. These criteria are introduced to avoid »floor effects«. There is no ideal model for dyskinesia severity assessment, but one recently published one seems very useful. Patients were observed for several hours with video recording, and blind assessment of dyskinesia severity by two independent neurologists was performed[33]. The primary endpoint is typically a dyskinesia and motor fluctuation assessment, usually a time spent in various motor stages (»on without dyskinesia«, »on with troublesome dyskinesia«, and »off« stage). Currently there are no medications labeled for the treatment of dyskinesia, although there are few randomized controlled trials (RCT) providing evidence that clozapine and/or amantadine might be useful as a short-term (i.e., a few months) treatment.

Development of drugs which will delay the development of dyskinesias or motor fluctuations

Special types of trials are those assessing the first time occurrence of dyskinesia and motor fluctuation in patients with early or advanced IPD. These studies are very long (up to 5 years), and randomized double blind placebo controlled parallel design is the standard. Studies usually involve the enrollment of several hundred patients, and therefore multiple centers are usually involved. A final visit shortly after drug-exposure cessation is standard for safety monitoring and allows the detection of withdrawal effects on primary and secondary outcomes. These studies enroll patients who at baseline are in need of symptomatic antiparkinsonian therapy. IPD patients must be newly in need of symptomatic anti-

parkinsonian therapy, typically Hoehn and Yahr Stage I–III. They should have no prior exposure or very minimal prior exposure to dopaminergic drugs and should not have motor fluctuations or dyskinesias at baseline. The study randomizes patients to standard dopaminergic therapy, usually levodopa, or the new study drug. Because these studies are long in duration, some protocols permit the addition of levodopa in both groups if inadequate efficacy of treatment is encountered in the midst of the study period. Primary endpoints typically include time to development of these complications and a percentage of the population at given time points that has the complication. Secondary endpoints include measures of parkinsonian impairment, such as UPDRS scores, Clinical Global Impressions of Severity and Change, and Quality of Life measures such as the PDQ-39 and PDQUALIF. Secondary endpoints can also include a neuroimaging outcome measuring the uptake of ligands specific to the dopamine system, such as [123I]β-CIT (2b-carbomethoxy--3β –[4-iodophenvl]) and single photon positron emission tomography (SPECT) or [18F]-dopa and positron emission tomography (PET) scanning indices. The analyses are based on the intention-to-treat strategy. All statistical tests are two-sided, and p-values <0.05 are considered statistically significant, though sometimes adjusted p-values are used to account for multiple comparisons. The primary analysis for studies involving delay in the development of motor complications uses a survival approach and calculates the cumulative probability of reaching each endpoint. Differences in outcome are expressed as hazard functions, usually with the Kaplan--Meier estimate, which can be displayed graphically. It is important to censor individuals who either drop out or have limited follow-up. Hypothesis testing between groups can use the log rank test or Cox's proportional hazard regression modeling, which allows adjustment for multiple covariates.

Development of drugs for non-motor symptoms of Parkinson's disease

Outside of the primary motor elements of IPD (parkinsonism and motor complications), PD patients experience a number of other disabilities, including sleep disorder, cognitive impairment, depression, apathy, hallucinations, dysautonomia, pain, bladder, bowel and sexual dysfunction, fatigue, and many others. Most of these symptoms worsen during the L-dopa »wearing-off« and »off« phases and have a dramatic effect on the lives of both PD patients and caregivers[34]. Non-motor symptoms of IPD are not well recognized in clinical practice, either in primary and secondary care. Depression, anxiety, fatigue, and sleep disturbance are among the most troubling symptoms for IPD patients, but during routine consultations, these symptoms are not identified by neurologists in over 50% of consultations. Sleep disturbance in particular is not recognized in over 40% of patients[35]. Interest is growing in the evidence based treatment of non-motor symptoms, but in part, its success will depend not just on the identification but also on the quantification of the effects of treatment on patients' baseline disability. Drugs that are useful in treating these symptoms in other medical contexts can be tested through randomized double-blind, placebo-controlled trials of IPD subjects with the target problem and appropriately designed measurement tools adapted from other medical fields. However it seems that symptom-specific instruments are still not validated and may not be relevant to people with IPD[36]. Regardless of instruments used, the analysis of efficacy variables is based on the intention-to-treat strategy, as previously mentioned.

Conclusion

Treatment aims in PD include the provision of symptomatic relief, reduction of functional disability, halting or slowing of the neurodegenerative process, and the prevention of long-term complications by proper initiation of therapy. At present, pharmacotherapeutic strategies allow the amelioration of motor symptoms of IPD only, whereas non-motor manifestations are not helped by dopamine replacement strategies. In addition, levodopa-induced fluctuation and dyskinesia are still challenging, particularly in long-term treatment. Despite advances in pharmacotherapy that have improved quality of life for these patients, the mortality rate remains largely unchanged. Recent studies have found that patients with Parkinson's disease have a two-fold to five-fold higher mortality rate than control subjects[37–38]. This is within the range of Hoehn and Yahr's observations from 1967[39]. Sustained interest in IPD will hopefully allow increased funding of research to develop new and better treatments.

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PARKINSONOVA BOLEST – IZAZOVI U RAZVOJU NOVIH LIJEKOVA

S A Ž E T A K

Idiopatska Parkinsonova bolest je nakon Alzheimerove bolesti, najčešća neurodegenerativna bolest. Ciljevi liječenja uključuju ublažavanje simptoma bolesti, smanjenje funkcionalne nesposobnosti, zaustavljanje ili usporenje neurodegenerativnog procesa i prevenciju dugotrajnih komplikacija inicijacijom odgovarajuće terapije. Sadašnje farmakoterapijske strategije dovode samo do olakšavanja motornih simptoma bolesti, dok nadomjesna dopaminska terapija nije učinkovita u liječenju ne-motornih manifestacija bolesti. Osim toga, levodopom inducirane fluktuacije i diskinezije predstavlju izazov za razvoj novih lijekova i to osobito u dugotrajnom liječenju. Unatoč napretku u farmakoterapiji idiopatske Parkinsonove bolesti koja je poboljšala kvalitetu života tih bolesnika, mortalitet je ostao i dalje nepromijenjen. Podržavanje zanimanja za idiopatsku Parkinsonovu bolesti pridonijet će razvoju nove i učinkovitije terapije.