Prospects for new drug treatment in idiopathic parkinsonism

Ali Samii, Shallen R. Letwin and Donald B. Calne

Parkinson's disease is one of the most common neurological disorders of the elderly. However, several recent drug developments have been made in the treatment of idiopathic parkinsonism (IP). The authors describe the most promising new drugs for treatment of the motor symptoms of IP, briefly discuss two promising monoamine oxidase inhibitors and review the newer medications for the treatment of the psychiatric symptoms associated with IP. They also survey some of the future therapeutic options in early stages of development.

The categories of drugs most widely used to alleviate the motor symptoms of idiopathic parkinsonism (IP) include the dopamine precursor levodopa combined with a peripheral decarboxylase inhibitor (carbidopa or benserazide), the artificial dopamine agonists, and the monoamine oxidase (MAO) inhibitors. But a new category of drugs has now become available, namely the inhibitors of the enzyme catechol-*O*-methyltransferase (COMT). These are described below, followed by a discussion of the newer artificial dopamine agonists. The application of these new drugs in the treatment of IP is summarized in Table 1.

COMT inhibitors

The metabolism of levodopa is affected primarily by three enzymes, dopa-decarboxylase, COMT and MAO. The majority of levodopa is metabolized in the peripheral tissues, leaving less than 1% to enter the brain[1], but if levodopa treatment is combined with a dopa-decarboxylase inhibitor, there is a substantial increase in the amount of levodopa available for entry into the brain. However, the metabolism of levodopa is also shunted towards COMT and MAO. COMT causes 3-*O*-methylation of levodopa and produces an active metabolite, 3-*O*-methyldopa. The exact role of 3-*O*-methyldopa is not fully understood; however, it has been investigated to determine whether it might aggravate or even improve parkinsonism[2]. It was initially thought that 3-*O*-methyldopa could act as a reservoir for levodopa and thus ameliorate parkinsonism by maintaining plasma levels[3], but other studies have suggested an antagonistic effect mediated through competition with levodopa for transport into the brain[4]. It has been proposed that some patients who experience dyskinesia and motor fluctuations also have increased levels of *O*-methyldopa in their brain, but no consistent relationship has been established[5–8].

COMT inhibitors have been studied since the late 1970s and they have been classified as either peripheral or central acting[9]. Peripheral-acting COMT inhibitors block the enzyme in tissues such as muscle, gut, kidney, liver and erythrocytes, whereas central-acting COMT inhibitors block the enzyme in the brain[9]. The two most promising COMT inhibitors are tolcapone and entacapone (Figure 1), both of which have significant benefits in patients with IP.

Tolcapone

Tolcapone is the most potent and selective COMT inhibitor identified to date. In animal models, tolcapone acts both centrally and peripherally, but in humans, it is not known whether the plasma concentrations reached are sufficient to elicit a central effect[9,10]. Several single-dose and short-term

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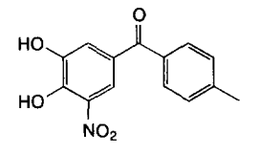
Table 1. New drugs used as adjunctive therapy with levodopa (or with possible application as monotherapy[a]) in the treatment of parkinsonism

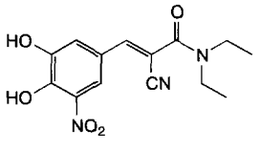
Drug name	Mechanism of action	Potential adverse effects	Recommended dosages
Tolcapone	Catechol-*O*-methyl-transferase inhibitor	All adverse effects of levodopa may be exacerbated, with the addition of diarrhea and liver enzyme elevation	300–600 mg daily, in 3–4 divided doses (liver enzymes must be checked prior to therapy, and every six weeks for the first six months)
Entacapone	Catechol-*O*-methyl-transferase inhibitor	Same as tolcapone	600–1200 mg daily, in divided doses, taken with levodopa
Pramipexole[a]	Non-ergoline dopamine agonist (preferentially at the D_3 receptor)	Side-effect profile similar to other doparnine agonists without ergot-related complications	Gradual (over several weeks) dose titration up to 4.5 mg day^{-1} in divided doses
Cabergoline	Ergoline derived, D_2 receptor dopamine agonist (long acting)	Side-effect profile similar to other ergot related dopamine agonists	Gradual (over several weeks) dose titration up to 5 mg day^{-1}, once-daily dosing
Ropinirole[a]	Non-ergoline D_2 receptor dopamine agonist	Side-effect profile similar to other dopamine agonists without ergot-related complications	Gradual (over several weeks) dose titration to between 3 and 24 mg day^{-1} in divided doses

[a]Possible use as monotherapy.

studies have measured the pharmacokinetic effects of levodopa when co-administered with tolcapone[10–13]. These effects include the area under the curve (AUC), the time to reach maximum concentration (T_{max}), the maximum concentration (C_{max}) and the half-life ($t_{½}$). Clinical measures also change, including the Unified Parkinson's Disease Rating Scale scores (UPDRS), hand-tapping test, walking test, and the duration of 'on' or 'off' time. After the administration of tolcapone, the AUC and the $t_{½}$ of levodopa increased, but the C_{max} and T_{max} remained unchanged. Tolcapone enhanced the duration of 'on' time by 14–77% in a dose dependent fashion, but this led to increased dyskinesia.



Tolcapone



Entacapone

Figure 1. *New catechol-O-methyltransferase inhibitors.*

A multicenter, double-blind, placebo-controlled trial studied 151 patients with IP who had predictable 'on' responses to the first morning dose of levodopa and predictable 'off' periods while awake[14]. This study included a two-week, single-blind, placebo baseline period, a ten-hour baseline assessment, and a double-blind period. Patients were then randomized to receive either placebo or tolcapone (50, 200 or 400 mg) three times a day (tid) together with levodopa. With all doses of tolcapone, a significant improvement in the 'off'-period durations, motor scores, total UPDRS scores, and the global assessments at six weeks was noted. These improvements allowed a significant reduction in the levodopa/carbidopa daily intake without aggravating motor symptoms.

In a larger double-blind, multicenter trial, 298 patients receiving levodopa but without motor fluctuations were given either placebo, 100 mg or 200 mg of tolcapone tid and their clinical progress was followed for up to a year[15]. At six and twelve months, both dosages produced significant improvements in activities of daily living scores and UPDRS motor scores and allowed a significant reduction in daily levodopa intake. Dyskinesia was slightly more prevalent in the two tolcapone groups than the placebo group, and only one patient taking the higher dose of tolcapone experienced severe dyskinesias. Diarrhea was the most important nondopaminergic adverse event – one patient in the placebo group withdrew because of diarrhea, compared with eight in the lower-dose group and five in the higher-dose group. Eight patients receiving tolcapone also had elevated liver enzymes, and four were withdrawn from the study because of it. The liver enzyme levels in the other four returned to normal during treatment.

In another placebo-controlled, double-blind study of 202 IP patients with the

'wearing off' phenomenon on levodopa[15], 200 mg tid of tolcapone significantly reduced 'off'-period duration and, as in previous studies, tolcapone treatment allowed a reduction in total daily levodopa intake. Dyskinesia developed or worsened in 51% and 64% of patients receiving 100 mg and 200 mg tid of tolcapone, respectively, compared with 18% of patients receiving the placebo. The most common non-dopaminergic adverse effect was diarrhea (19% of patients taking 200 mg tid), although this complication also occurred in 14% of patients receiving the placebo. Asymptomatic elevations in liver enzymes occurred in five patients, three in the 100 mg tid group, and two in the 200 mg tid group. As a result, one patient from the latter group was withdrawn from the study.

Tolcapone – summary. Tolcapone can be beneficial as adjunct therapy with levodopa in patients with or without motor fluctuations. It prolongs 'on' time but can exacerbate all levodopa-induced complications, including dyskinesia. It is probably most useful in patients experiencing the 'wearing off' phenomenon by prolonging the action of levodopa. It may cause diarrhea and asymptomatic elevation of liver enzyme levels, hence, liver function should be checked regularly for the first few months of therapy with tolcapone.

Entacapone

Entacapone differs from tolcapone because it does not enter the brain as readily[9]. The single-dose trials have reported an increase in plasma AUC and $t_{½}$, and a slight increase or no change in the C_{max} and T_{max} of levodopa[17,18]. These studies indicated that entacapone improved certain motor functions, but the overall global assessment was not significantly different from placebo. There was an increase in dyskinesia with entacapone which seemed to be dose dependent. In a study involving 12 healthy volunteers[19], entacapone was given in single doses ranging from 100 to 800 mg together with controlled-release levodopa/carbidopa. There was an increase in the AUC and a slight increase in the C_{max} of levodopa but no change in the T_{max}, and no major adverse reactions.

In an open-label study[20], entacapone (200 mg 3–4-times daily) was added to the usual levodopa/benserazide dose of nine patients with IP. After the addition of entacapone, a 16% decrease in clinical disability was observed. The AUC of levodopa increased by ~40% without any changes to the C_{max} or T_{max}. In addition, the AUC of 3-O-methyldopa and homovanillic acid (products of dopamine degradation) decreased. Only mild adverse effects were reported, including nausea, diarrhea, headache and fatigue. In another open-label study[21], 12 patients received entacapone (800–1200 mg day^{-1}) along with their standard levodopa/carbidopa dose. The mean 'on' time increased by 48% and the AUC of levodopa increased by 21%. A significant increase in the duration of dyskinesia was observed in this study, which may have been caused by the higher doses of entacapone employed.

In a double-blind, placebo-controlled trial, 20 patients were randomized to receive a single dose of entacapone (50–400 mg) or placebo along with a standard dose of levodopa/carbidopa[22]. There were five treatment periods, each lasting 24 hours, and a week-long washout between each administration. The AUC of levodopa increased proportionally with entacapone up to 200 mg, but beyond that dose, there was no further change. The C_{max} of levodopa did not change, but the $t_{½}$ increased significantly with rising doses of entacapone. Only the 200 mg dose of entacapone significantly increased the mean 'on-time' compared with placebo. During the baseline assessment, all patients experienced dyskinesia on levodopa/carbidopa alone (mean duration = 147 min), and there was a significant increase (32%) in the duration of dyskinesia with the 200 mg dose of entacapone. A similar increase also occurred with the 400 mg dose. Most patients reported mild adverse effects such as nausea, flatulence, headache, faintness and fatigue.

In another double-blind, placebo-controlled study, 26 patients taking levodopa with either carbidopa or benserazide were randomized to receive 200 mg of entacapone 4–10-times daily or placebo[23]. This study was conducted over a four-week period, after which the treatment groups were crossed over. The AUC of levodopa was increased, the $t_{½}$ was significantly prolonged (by 32%), but the T_{max} and C_{max} remained unchanged. Entacapone significantly increased the duration of the 'on' periods (by 24%) and the duration of dyskinesia (by 32%). In these two trials, no significant abnormalities were found in extensive laboratory tests.

Entacapone – summary. When co-administered with levodopa preparations, entacapone also improves motor fluctuations by prolonging the 'on' time, but it exacerbates levodopa-induced adverse affects, such as dyskinesia. This drug appears promising in the treatment of patients who experience frequent end-of-dose 'off' periods and, in contrast to tolcapone, liver enzyme elevation is not a significant concern.

Artificial dopamine agonists

Artificial dopamine agonists stimulate dopamine receptors directly, without the need for uptake and conversion to dopamine by the presynaptic neuron. These agonists are not as effective as levodopa in relieving the motor symptoms of IP, but the addition of dopamine agonists to levodopa or the partial replacement of levodopa with dopamine agonists can significantly reduce motor fluctuations and especially dyskinesia[24]. In addition, the early use of dopamine agonists alone or in combination with levodopa for treatment of IP has been advocated[25]. However, one recent prospective, double-blind, randomized study failed to show that early bromocriptine/levodopa combination therapy can prevent motor fluctuations[26]. Currently available dopamine agonists include bromocriptine, pergolide, lisuride and apomorphine. The commonly used dopamine agonists (bromocriptine, pergolide, and lisuride) are ergot derivatives that can rarely result in pleuropulmonary complications. Dopamine agonists that are not structurally related to ergot (pramipexole and ropinirole) are now available, and there is also a new very-long-acting ergot derivative, cabergoline (Figure 2). These are discussed below.

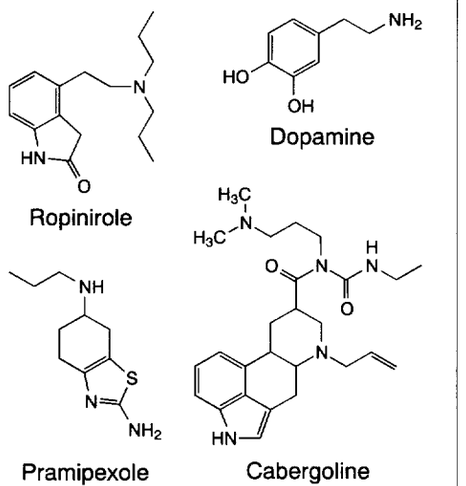


Figure 2. *Dopamine and some new artificial agonists.*

Pramipexole

Pramipexole is a synthetic aminobenzathiazol derivative that has agonist activity at the presynaptic and postsynaptic dopamine receptors belonging to the D_2 subfamily. It differs from bromocriptine, pergolide and lisuride because of its preferential affinity to the D_3 receptor subtype within the D_2 receptor subfamily[27–29]. The neuroendocrine effects of pramipexole are similar to those of other D_2 receptor agonists[30].

In a small single-blind trial involving 24 patients with advanced IP and motor fluctuations[21], pramipexole or placebo was administered as adjunctive therapy with levodopa. Pramipexole was titrated up to 4.5 mg day^{-1} over seven weeks, followed by a three-week maintenance period. The pramipexole-treated patients experienced a significant improvement in their 'off' period activities of daily living scores, but the motor-score improvement did not reach statistical significance, perhaps because of the small size of the study. The daily levodopa intake was significantly reduced in the pramipexole treated group, and the adverse effects were similar to those of other dopamine agonists.

In a small multicenter, double-blind, placebo-controlled trial of pramipexole, 55 patients with early IP were studied[32]. The patients received 10 mg selegiline (an inhibitor of MOA-B) daily throughout the course of the trial, but they did not receive levodopa. Pramipexole or placebo were administered in an ascending dose schedule for the first six weeks, and maintained at the highest tolerated dose (up to 4.5 mg day^{-1}) for three weeks. The pramipexole-treated patients showed significant improvement in their activities of daily living during the maintenance period. The motor improvement in the pramipexole-treated group was 44% more than that in the placebo-treated group, but this difference did not reach statistical significance, perhaps because of the small number of patients.

In a larger double-blind, multicenter trial involving 335 patients with early IP (Ref. 33), pramipexole or placebo were administered according to an ascending-dose schedule (up to 4.5 mg day^{-1}) for the first seven weeks. Approximately two-thirds of the patients in each group were receiving selegiline, but none were receiving levodopa. They were maintained on the highest tolerated dose for six months, followed by a one-week dose-reduction phase. The mean daily maintenance dose was 3.8 mg. There were significant improvements in activities of daily living scores and UPDRS motor scores in the pramipexole group compared with the placebo group, although nausea, insomnia, constipation, somnolence, and visual hallucinations occurred significantly more frequently in the pramipexole group. Orthostatic hypotension was seen in 10% of pramipexole- and 6% of placebo-treated subjects, but the incidence of symptomatic orthostatic hypotension did not differ between the two groups.

In another multicenter, placebo-controlled, double-blind study with 360 advanced IP patients receiving levodopa, pramipexole was compared with placebo as adjunctive therapy[34]. Pramipexole was titrated to 4.5 mg day^{-1} during the first seven weeks, followed by 24 weeks of treatment on

the maintenance dose. Pramipexole improved motor function during both the 'on' and 'off' periods, decreased 'off'-period duration, and allowed a reduction in levodopa dosage. The side-effect profile of pramipexole in this study was typical of the profiles of other dopamine agonists.

In a recent multicenter, double-blind trial involving 247 advanced IP patients with 'wearing off' phenomenon[35], pramipexole and bromocriptine were compared with each other and with placebo as adjunctive therapy together with levodopa. The maximum doses were 4.5 mg day^{-1} for pramipexole and 30 mg day^{-1} for bromocriptine. The dose-escalation period lasted up to 12 weeks, and the dose-maintenance period lasted up to 24 weeks. Both drugs showed significant improvements in activities of daily living scores and UPDRS motor scores over placebo, although the beneficial effects of pramipexole appeared more robust numerically. Direct comparisons between the two drugs revealed a trend of superiority of pramipexole over bromocriptine, but this trend did not reach statistical significance. The rates of adverse effects between the two drugs were similar, and the dropout rates were identical at 20%. There was, however, a 40% dropout rate in the placebo group because of exacerbating parkinsonian symptoms during the trial.

Pramipexole – summary. Pramipexole can be useful in the treatment of early and advanced IP, with the added advantage of not being an ergot derivative. Nevertheless, large trials directly comparing pramipexole monotherapy and levodopa monotherapy, and additional studies comparing the efficacy of pramipexole to other dopamine agonists as adjunct therapy are still needed to define its role in treating IP fully.

Ropinirole

Ropinirole is a potent and highly selective, non-ergoline D_2 receptor agonist that has been reported to be effective in treating the motor symptoms of IP (Refs 48–54). In a small open-label study of only 6 patients with IP (stage 3–4), ropinirole was found to be as effective as levodopa when given alone in single doses of >4 mg (Ref. 49). Both motor improvement and adverse effects were dose dependent.

A double-blind, placebo-controlled study was undertaken to evaluate the role of ropinirole as adjunct therapy in the treatment of 46 patients with IP receiving levodopa[51]. Detailed diaries and Clinician's Global Evaluation scores were used to assess efficacy, and no objective motor testing was performed. There was a significant reduction in the duration of 'off' periods as assessed by diary cards. The adverse effects experienced by patients in the ropinirole group were similar to those caused by other dopamine agonists.

In a large double-blind, multicenter trial involving 241 patients with early IP (Ref. 54), patients were assigned to receive either placebo or ropinirole. Approximately half of the patients in each group were on selegiline, but none were receiving levodopa. The starting dose was 0.25 mg tid, with titration to at least 1.5 mg tid. A 24% improvement in UPDRS motor scores in the ropinirole group was found, compared with a 3% worsening in the placebo group. Twice as many patients withdrew from the ropinirole group because of adverse effects compared with the placebo group, and the most common adverse effects were nausea, dizziness and somnolence. The incidence of neuropsychiatric side effects was quite low in this study.

Ropinirole – summary. Ropinirole is a promising new dopamine agonist with the advantage of not being an ergot derivative. Further studies are needed to compare its efficacy directly with that of other dopamine agonists as monotherapy or adjunct therapy in IP.

Cabergoline

Cabergoline is a new ergot derivative with high affinity for the D_2 receptors and a longer duration of action than bromocriptine, pergolide or lisuride[36,37]. Cabergoline was first reported as an effective long-lasting prolactin-lowering agent[38,39], with subsequent open-label studies showing beneficial effects in the treatment of IP (Refs 36,40,41). The latest of these reports found cabergoline to be safe and well tolerated in the long term[41]. Several controlled studies have recently reported the efficacy of cabergoline in parkinsonian motor symptoms[42–46].

In one study comparing cabergoline with placebo as adjunctive therapy in IP, a significant improvement occurred in motor scores with cabergoline in doses up to 5 mg day^{-1} (but not with placebo) and even persisted 48 hours after the last cabergoline dose[44]. In a subsequent open-label, dose-escalation phase, further improvement occurred without exacerbating dyskinesias. In a double-blind comparison of cabergoline and bromocriptine added to pre-existing levodopa, cabergoline given as a single morning dose was at least as effective in treating motor symptoms as bromocriptine administered tid[46].

In a larger (188 patients) placebo-controlled trial of once-daily cabergoline as adjunctive therapy[45], activities of daily living and motor scores improved significantly. The daily

levodopa dose was reduced by 18%, and the time spent in the 'on' state increased in the cabergoline-treated patients. The side-effect profile of cabergoline is similar to that previously reported for other ergoline-related dopamine agonists, including pulmonary reactions[47].

Cabergoline – summary. Cabergoline appears to be as effective in treating the motor symptoms of IP as bromocriptine, when administered as adjunctive therapy. Where compliance is a problem, cabergoline has the advantage of a good response with only one dose per day, but unfortunately, it is an ergot derivative and may cause ergot-related side effects.

MAO inhibitors

MAO is the main enzyme involved in the intracellular breakdown of monoamines (dopamine, norepinephrine and serotonin) in the brain[55]. MAO-A inhibitors have been used to treat depression for the past 30 years. MAO-B inhibitors impede the breakdown of dopamine in the basal ganglia. Selegiline, a selective, irreversible MAO-B inhibitor, has been used as an antiparkinsonian agent. Initially, it was hoped that selegiline might have a neuroprotective action, because of a theoretical argument that dopamine turnover might damage neurons by leading to an excess of free radicals[56]. Although selegiline has been shown to have some antiparkinsonian benefits[57], these effects are probably secondary to symptomatic relief rather than neuroprotection[58,59]. In addition, recent studies have cast doubts on the efficacy and safety of selegiline[60–62]. Given the controversies surrounding selegiline, the role of MAO inhibitors in the treatment of IP is likely to remain controversial. However, two recently tested MAO inhibitors merit mentioning – lazabemide and moclobemide, which inhibit MAO-B and MOA-A, respectively.

Lazabemide

Lazabemide is a reversible MAO-B inhibitor that is 100-times more selective in blocking MAO-B than selegiline[63]. In one placebo-controlled, multicenter trial of 201 previously untreated patients with IP, lazabemide resulted in a significant improvement in the activities of daily living scores after four weeks, and it was tolerated as well as the placebo[64]. In another placebo-controlled trial of lazabemide as adjunct therapy in 137 patients already treated with levodopa, lazabemide was well tolerated, but no significant clinical improvement occurred after 4 weeks of treatment when compared with placebo[65]. In a recent multicenter study, the clinical progress of 321 patients with early untreated IP who received different doses of lazabemide (25–200 mg day^{-1}) was followed for one year[66]. Lazabemide was well tolerated in this study and reduced parkinsonian symptoms. All dosages were similar in efficacy, and the magnitude of benefits were similar to those seen after one year of selegiline treatment in the DATATOP trial[57]. In all three placebo-controlled studies, there were no significant changes in vital signs at any visit, implying little, if any, unwanted effects on blood pressure.

Moclobemide

Moclobemide is the first member of the reversible MAO-A inhibitor class of antidepressants and, compared with the irreversible MAO-A inhibitors, it is much less likely to produce the cardiovascular 'cheese effect' (i.e. potentiation of the sympathomimetic action of indirectly acting amines such as tyramine, found in cheese)[67]. The ingestion of up to 100 mg of tyramine with food produced no significant pressor effect even with high doses of moclobemide (600 mg day^{-1})[68]. Moclobemide has been studied in double-blind, placebo-controlled trials for the treatment of depression[69]. In one comparison of moclobemide, amitriptyline and placebo, both drugs were found to be more effective than placebo in treating depression, with moclobemide having fewer side effects (including the absence of any significant cardiovascular side effects)[70]. A meta-analysis of studies with moclobemide suggests that elderly depressives do as well as younger patients taking moclobemide, while younger patients do better with classical antidepressants[71]. In one uncontrolled study of only 12 euthymic patients with IP, the latencies of motor responses after single-dose levodopa challenges were significantly shortened and their durations were prolonged after three weeks of moclobemide treatment[72]. In addition, the motor scores after overnight withdrawal of dopaminergic medication improved on moclobemide. However, three of the 12 patients had a postural drop of 20 mm Hg in systolic blood pressure, with one of them experiencing orthostatic lightheadedness. The investigators concluded that moclobemide may be a useful antidepressant in patients with IP; however, these subtle findings in patients who are not depressed are insufficient to justify the use of moclobemide in treating the motor symptoms of IP.

Larger placebo-controlled trials in depressed patients with IP are necessary to determine the role of moclobemide in IP as an antidepressant/antiparkinson agent. In addition, the incidence of orthostatic hypotension in patients on moclobemide together with antiparkinsonian medications needs to be determined in controlled trials.

Antidepressants

Depression is a common problem in IP. Most classical antidepressants produce significant anticholinergic/antihistaminergic side effects. Another major issue in IP is medication-induced hypotension, which may be exacerbated by many antidepressants. The combined hypotensive effects of antiparkinsonian and antidepressant medications can cause symptoms severe enough to warrant the use of mineralocorticoids or vasoconstrictor agents. A new antidepressant, venlafaxine, has been found to be beneficial in IP, specifically with regards to hypotension.

Venlafaxine

Venlafaxine inhibits the neuronal uptake of serotonin and norepinephrine and, to a lesser extent, dopamine, with much lower anticholinergic/antihistaminergic activity than tricyclic antidepressants[73]. In controlled trials, venlafaxine was equal to trazodone[74] and slightly better than imipramine[75] and fluoxetine[76] in treating depression. Nausea is the main side effect of venlafaxine but tends to occur early in the course of treatment and is usually resolved with continued therapy[75,77]. Nausea can be minimized by starting with lower doses and slowly increasing the daily intake divided into two or three doses taken with food[77]. There are no reports of significant hypotension associated with venlafaxine. In fact, dose-dependent blood-pressure elevation has been reported in some patients[78]. Sustained diastolic blood-pressure elevation of up to 10% above baseline was observed in 7% of patients receiving 200–300 mg day^{-1}, and in 13% of patients receiving >300 mg day^{-1} (Ref. 78). Although the efficacy of venlafaxine in treating depression in IP has not been formally studied in a controlled trial, it seems to be as effective as, if not superior to, other antidepressants in non-parkinsonian patients. In addition, the potential effects of venlafaxine on blood pressure may be helpful in treating patients with IP suffering from depression and hypotension.

Neuroleptics

Although psychosis may be a complication of IP itself, it is usually an adverse effect of levodopa preparations or dopamine agonists. Medication-induced psychosis places the patient and the clinician in a difficult situation. On one hand, decreasing the dose of levodopa or the dopamine agonist may alleviate the psychiatric symptoms but, on the other hand, worsening of parkinsonian motor symptoms may occur. As expected, typical neuroleptics such as haloperidol, which primarily block dopamine D_2 receptors, would have a devastating effect on the motor symptoms of patients with IP. Fortunately, clozapine and, more recently, olanzapine have been shown to be effective in ameliorating hallucinations[79,80].

Clozapine

Clozapine, a dibenzazepine analog, has been the drug of choice in patients with medication-induced psychosis because of its ability to alleviate these symptoms without precipitating parkinsonian motor symptoms[79,81,82]. The initial starting dose for medication-induced psychosis in patients with IP is generally 6.25 mg day^{-1}. The dose can be slowly increased until a response occurs. Most patients will respond to doses in the range of 25–50 mg day^{-1} (Ref. 79), which is significantly lower than the average dose required to treat schizophrenia (300–600 mg day^{-1}). Unfortunately, there is a 1% risk of developing agranulocytosis with clozapine and, thus, weekly blood monitoring is required.

Olanzapine

Olanzapine is a new, atypical antipsychotic medication with similar dopamine-receptor-affinity profiles to clozapine. Also, its clinical profile is comparable with that of clozapine[80] and, to date, there has been no published case of agranulocytosis with it. An open-label trial has studied the efficacy of olanzapine (2–15 mg day^{-1}) in alleviating psychotic symptoms in 15 patients with IP (Ref. 80). In this study, the doses of all dopaminergic medications were reduced to the lowest acceptable level, with the dose remaining stable for five days before starting olanzapine. The patients then received increasing doses of olanzapine, which was titrated over 42 days. On day 50, the doses of the dopaminomimetic agents were increased to improve motor symptoms. The patients were assessed using the UPDRS and the Brief Psychiatric Rating Scale. Psychotic symptoms improved dramatically in all patients without aggravation of their motor symptoms. The mean daily dose achieved was 6.5 ± 3.9 mg day^{-1}.

In summary, olanzapine has proved to be beneficial and well tolerated in the treatment of drug-induced psychosis in patients with IP. As it does not seem to worsen extrapyramidal symptoms nor require regular blood monitoring, olanzapine may have more advantages than clozapine in treating psychosis in patients with IP.

N-Methyl-D-aspartate receptor antagonists

The exact role of the major excitatory neurotransmitter glutamate in the pathogenesis of IP, and the interactions

between glutamate and dopamine in the basal ganglia, are still being explored[83–87]. Based on simplified anatomical models of basal ganglia, an over-active subthalamic nucleus, which uses glutamate as a neurotransmitter, is believed to play a role in the production of parkinsonian motor signs[88,89]. In addition, glutamate excitotoxicity has been implicated in the pathogenesis of IP (Refs 86,87,90). Therefore, in theory, glutamate receptor antagonists may be beneficial not only in treating the motor symptoms of IP but also in neuroprotection and slowing disease progression.

The *N*-methyl-D-aspartate (NMDA) receptor is the best-characterized subtype of the glutamate receptors, and specific antagonists for this receptor subtype have been designed[91]. In animal models, NMDA antagonists have been shown to protect the substantia nigra from the toxic effects of 1-methyl-4-phenylpyridium ions (MPP^+)[92]. Amantidine and memantine are 1-amino-adamantanes that act at the phencyclidine (PCP) binding site of the NMDA receptor, and both have been used to treat the motor symptoms of IP (Refs 93,94). Small, human studies using these two drugs and other NMDA receptor antagonists, such as lamotrigine and ifenprodil, to treat the motor symptoms of IP have shown either no significant benefit or marginal benefit[94–96]. Unfortunately, efforts aimed at modulating glutamatergic transmission in humans have not yet produced a drug nearly as effective in treating the motor symptoms of IP as levodopa or dopamine agonists.

Neurotrophic factors

Another neuroprotective approach to treating IP is the use of trophic factors to nourish and enhance the survival of dopaminergic cells in the substantia nigra. Several of these factors, including neurotrophin-4/5 (NT-4/5)[97], brain-derived neurotrophic factor (BDNF)[98–100] and glial-cell-line-derived neurotrophic factor (GDNF)[101–107], have been identified and shown to be promising in animal models of IP.

In one study, after two weeks of supranigral infusion via a posterior fossa cannula in rats, NT-4/5 and BDNF raised dopamine turnover both metabolically (i.e. increased homovanillic acid production) and through the release of dopamine pools[97]. In another experiment, intrastriatal injections of BDNF in rats followed by intrastriatal injections of 6-hydroxydopamine (a toxin selective for dopaminergic neurons) led to the presence of a halo of dopaminergic axons at the BDNF injection site[99]. The authors concluded that BDNF demonstrates neuroprotective activity by attenuating the toxic effects of 6-hydroxydopamine on dopaminergic neurons.

GDNF was identified using embryonic neurons from the ventral mesencephalon in a search for a neurotrophic factor for dopaminergic cells in the substantia nigra[108]. The neuroprotective effects of GDNF on neurotoxin-mediated cell death have been well documented[102–104,109]. In animal studies involving 6-hydroxydopamine-lesioned rats[107] and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-lesioned monkeys[110], intraventricular or intracerebral GDNF injections actually improved motor function. A multicenter human study of GDNF is expected to begin soon. In this study, GDNF will be delivered to the intraventricular cavity of parkinsonian patients using a surgically implanted cannula. The results should help to define the role of neurotrophic factors in the treatment of IP.

Gene therapy

The introduction of genetic material into the nervous system of patients with IP may follow different functional strategies[111–113]. First, gene therapy could potentially replace a defective gene. Unfortunately, efforts aimed at identifying specific genetic defects have failed to produce a universally defective gene in IP. Therefore, there are no current candidate genes for replacement or knockout in IP.

The second potential strategy would be the introduction of a functional gene that would increase the amount of dopamine in the striatum. This has been performed successfully in animal models by introducing the tyrosine hydroxylase gene into the nervous system[114–116]. Tyrosine hydroxylase is the rate-limiting enzyme in the synthesis of dopamine, and its introduction into the striatum of IP patients could provide higher striatal dopamine levels. Of course, the augmentation of striatal dopamine levels is already being done pharmacologically through the use of levodopa. However, continuous intracerebral production of dopamine would provide more-stable dopamine levels with less pharmacokinetic fluctuation, and this could potentially reduce or even eliminate the systemic adverse effects of levodopa[117].

The third strategy would be to introduce the genes for neurotrophic factors into the CNS using viral vectors. Astrocytes or fibroblasts genetically engineered to produce neurotrophic factors have been successfully grafted in rat brains[106,118,119]. This could serve as a continuous source of GDNF or BDNF but, as mentioned earlier, the potential role of neurotrophic factors has yet to be defined in humans with neurodegenerative disorders.

Local immunosuppression for tissue transplantation

The transplantation of cells into the nervous system to treat neurodegenerative disorders has received much attention in the past few years[120–123]. Immunological modulation, for instance administering the systemic immunosuppressant cyclosporin A (CsA), is frequently used to support graft survival after transplantation[124].

Recently, Sertoli cells were shown to have local immunosuppressive activity[125–128]. Sertoli cells are highly differentiated non-germ cells found in the testis, which is considered to be an 'immunologically privileged' organ[129]. Sertoli cells produce an immunosuppressant factor, called Fas ligand[127]. Rat (allografts) or porcine (xenografts) Sertoli cells survived for two months after transplantation into the rat brain without CsA, suggesting that these cells provide adequate local immunosuppression for their own survival[126]. In one study, Sertoli cells transplanted into the rat striatum suppressed microglial activation and promoted the survival of simultaneously transplanted bovine adrenal chromaffin cells[125]. In another study, transplantation of Sertoli cells ameliorated behavioral deficits in 6-hydroxydopamine-lesioned rats, even without co-transplantation of other cells[128]. These findings would suggest that, in addition to their local immunosuppressive activity, Sertoli cells have a trophic effect on the surviving nigrostriatal dopaminergic neurons. The discovery of cells capable of providing local immunosuppression as well as trophic activity makes cell transplantation a promising future alternative in the treatment of IP.

Summary

Several new drugs have been approved for use or are currently in the final stages of investigation in the treatment of IP. The COMT inhibitors, tolcapone and entacapone increase the duration of action of levodopa, thus prolonging the 'on' periods but increasing dyskinesia. Pramipexole and ropinirole are non-ergot dopamine agonists that appear to be effective as adjunct therapy in IP. Cabergoline is a long-acting ergot derivative that improves motor symptoms when taken only once daily. Lazabemide is a reversible MAO-B inhibitor that improves motor symptoms but, similar to selegiline, its role as a neuroprotective agent remains controversial. Moclobemide is a reversible MAO-A inhibitor and an antidepressant that was found to improve motor symptoms in non-depressed patients with IP. Larger studies need to evaluate the role of moclobemide as a dual action (antidepressant and antiparkinsonian) drug in IP. Venlafaxine is an antidepressant with minimal anticholinergic/antihistaminergic side effects, and at higher doses, it can increase blood pressure, which may be helpful in patients with hypotension. Clozapine is effective in treating medication-induced psychosis without aggravating motor symptoms, but the risk of agranulocytosis warrants regular blood checks. Olanzapine is a new neuroleptic with no reported cases of agranulocytosis, and it is effective in reducing psychosis without adverse motor effects. NMDA antagonists have marginal benefits in treating the motor symptoms of IP, and their role as neuroprotective agents needs to be explored in human studies. The research on the potential uses of neurotrophic factors, gene therapy and local cellular immunosuppression for transplantation is still in its infancy. Further studies are needed to evaluate their safety and efficacy in humans with neurodegenerative disorders.

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