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Antiparkinsonian Agents

Clinically Significant Drug Interactions and Adverse Effects, and Their Management

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Summary

The treatment of Parkinson's disease for most patients entails long term exposure to multiple agents, including anticholinergics, levodopa, amantadine, dopamine receptor agonists, catechol-*O*-methyltransferase inhibitors, selegiline (deprenyl) and clozapine. Patients with Parkinson's disease require medication for the control of the motor symptoms of their condition, for related medical or psychiatric symptoms of the disorder, and for concurrent medical problems, such as hypertension or cardiac disease.

All these agents may cause adverse effects. There is a potential for drug-drug interactions between different antiparkinsonian agents and between antiparkinsonian medication and the other drugs a patient may be taking. Clinicians

caring for patients with Parkinson's disease must be knowledgable about the potential adverse effects and drug interactions of an expanding array of medications for this condition.

Parkinson's disease is a common degenerative disorder, affecting 1 in 300 individuals over 40 years of age.[1] Numerous agents are available for the treatment of the disease, and most patients face the prospect of taking one or more medications for several decades. For example, at the Center for Parkinson's Disease at Columbia-Presbyterian Medical Center, New York, US, with a patient population of >4000 individuals, over 90% of these patients are taking 2 or more medications. The use of medication for all ailments increases with age, and is correlated with the high incidence of chronic medical illness in the elderly, including cardiovascular disease, hypertension, diabetes mellitus and rheumatological conditions.[2] Therefore, in patients with Parkinson's disease, there is a potential for drug interactions between different antiparkinsonian agents, or between antiparkinsonian agents and drugs taken concurrently for other conditions.

Drug interactions may potentiate or antagonise the effect of antiparkinsonian agents, alter their pharmacological profiles, or influence the other medications a patient with Parkinson's disease may be taking. Drug interactions involving antiparkinsonian medications are unpredictable and have rarely been studied in a systematic way; much of the literature on this topic consists of case reports and published letters. For newer agents, clinical experience has been insufficient to identify important drug interactions. *In vitro* analyses of drug interactions do not allow predictions of clinical effects in patients. In 1 study evaluating the inhibitory effect of 4 dopamine agonists (bromocriptine, pergolide, pramipexole and ropinirole) on 6 human cytochrome P450 enzyme systems, the drugs differed from each other, but the clinical relevance could not be determined.[3] There are few pharmacokinetic studies of antiparkinsonian agents in humans, and most that are available involved healthy volunteers who were taking no concurrent medication. As such, recognising adverse drug interactions is a task that often falls to the clinician. Clinicians should, therefore, be aware of the potential drug interactions that can occur in patients with Parkinson's disease, and this has been the subject of a recent review.[4]

The purpose of this review is to discuss currently available medications for Parkinson's disease and to describe important undesired drug interactions and adverse effects that may occur in patients taking these medications. The article is intended to provide a practical guide for the clinician, rather than to give an exhaustive discussion of all interactions between antiparkinsonian agents and other medications that a patient with Parkinson's disease may be administered. In addition, approaches to the management of adverse reactions arising from antiparkinsonian medications are provided. The drugs under discussion include anticholinergics, dopamine receptor agonists, catechol-*O*-methyltransferase (COMT) inhibitors, amantadine, levodopa, selegiline (deprenyl) and clozapine.

References were gathered by performing a search of Medline using individual drugs as subject categories. The search was further expanded, where appropriate, by reviewing the original articles and their reference lists.

1. Pharmacotherapy of Parkinson's Disease

Patients with Parkinson's disease take medications for a number of reasons: (i) to prevent disease progression; (ii) to suppress the symptoms of parkinsonism; (iii) to reduce the complications of treatment, such as psychosis, motor fluctuations and dyskinesias; and (iv) to treat concurrent medical or psychiatric problems. Parkinson's disease is associated with a high incidence of psychiatric disorders, such as anxiety, depression, hallucinosis and sleep disturbance. Medical problems in patients with Parkinson's disease include orthostatic

hypotension, constipation, bladder problems and sexual dysfunction, all of which may necessitate direct medical treatment. In addition, patients may often have other medical problems that are common in individuals over 50 years of age, such as hypertension, coronary artery disease or arthritis.

At present, no agents are available that can prevent the progression of Parkinson's disease, or reverse its course. Because the cause and pathogenesis of the disease are unknown, aetiology-specific treatment is not feasible. Indirect evidence implicates selective oxidative injury to dopaminergic neurons as a possible cause. Therefore, neuroprotective therapy using antioxidants has been advocated, and the monoamine oxidase B (MAO-B) inhibitor selegiline (see section 1.5 has been studied in this regard. Symptomatic treatment for Parkinson's disease includes anticholinergics [such as trihexyphenidyl (benzhexol) and biperiden; see section 1.1] and dopaminergic agents (such as levodopa, amantadine and dopamine receptor agonists; see sections 1.2 to 1.4).

The aim of treatment in Parkinson's disease is to provide clinical benefit, while keeping adverse effects to a minimum. For most patients, the primary factor that limits medication dosage is the development of unwanted adverse effects. For example, anticholinergic medication may cause dry mouth, urinary retention, constipation and cognitive effects. Dopaminergic agents, such as levodopa and dopamine agonists, which are the mainstay of treatment for patients with Parkinson's disease, may cause dyskinesias, nausea, hypotension, hallucinations, somnolence and other symptoms. Drug interactions can also result in unwanted effects. Medications that interfere with the absorption of dopaminergic agents or counteract their mechanism of action may undermine the efficacy of antiparkinsonian treatment, while medications that enhance the effect of dopaminergic medications, such as COMT inhibitors, can increase their toxicity. In many cases, the drug interaction is not a pharmacokinetic interaction between one drug and the absorption, metabolism or excretion of another, but rather a direct cumulative or antagonistic effect of the two drugs.

Patients with Parkinson's disease vary in their susceptibility to the potential adverse effects of medications. When a drug interaction or adverse effect occurs in a patient taking more than one antiparkinsonian drug, it is often not clear which drug is the culprit, because both agents may share a similar pharmacological and adverse reaction profile. Pharmacological monitoring of drug concentrations of antiparkinsonian agents is not done and there is little information regarding the way these drugs are affected pharmacokinetically by other agents. Parkinson's disease itself, or age-related changes in metabolism and physiology, may also contribute to the production of adverse drug effects and drug interactions.

1.1 Anticholinergics

The first effective treatment for the symptoms of Parkinson's disease was the anticholinergic agent atropine, derived from the plant *Atropa belladonna*.[5] Anticholinergics were the mainstay of treatment for almost a century until the seminal report of levodopa, the prototype dopaminergic agent, in 1967.[6] Commonly employed anticholinergic drugs include trihexyphenidyl, benzatropine (benztropine), profenamine (ethopropazine) and biperiden.

Muscarinic cholinergic receptors are distributed throughout the CNS, including the basal ganglia. The selective degeneration of striatonigral neurons in Parkinson's disease is considered to result in a relative overactivity of cholinergic output from the basal ganglia, one consequence of which is tremor. Anticholinergic medications tend to be more effective in reducing tremor than rigidity, bradykinesia and postural instability. These drugs are also helpful in diminishing the drooling that occurs as a result of excessive salivary secretion in some patients with Parkinson's disease.

Anticholinergic agents may produce a muscarinic anticholinergic syndrome, whether used as monotherapy or concomitantly with other drugs that also have anticholinergic effects. Cognitive ad-

verse effects include confusion, impaired memory, delirium, hallucinations and psychosis, symptoms to which the elderly are especially predisposed.[7] The cognitive effects may be extremely subtle, such as mild memory impairment or decreased mental acuity, and may be observable only by family members. In patients with even mild dementia, anticholinergics may precipitate a serious confusional state. In severe cases, seizures may occur. Peripheral adverse effects of anticholinergic agents include dry mouth, blurred vision, constipation, urinary retention, tachycardia, hyperpyrexia and exacerbation of narrow angle glaucoma.

Patients with Parkinson's disease may be prescribed drugs that have anticholinergic properties for the treatment of other medical problems, including asthma, irritable bowel syndrome, depression and bladder disturbances. It is therefore important to recognise the clinical features of anticholinergic toxicity and be aware of the various medications, including over-the-counter (OTC) agents, that possess anticholinergic activity. Several of these are listed in table I.

The most important drug interaction between anticholinergics and other antiparkinsonian agents is a reduction in gastrointestinal motility, which affects drug absorption. Anticholinergics can reduce the bioavailability of levodopa[8,9] by delaying gastric emptying. This increases the extent of peripheral metabolism of levodopa by the gastric mucosa, so that less drug is available for absorption in the small intestine.[10] As such, there is also a potential for levodopa toxicity if anticholinergics are withdrawn.

Awareness of potential adverse effects and drug interactions will help avoid serious complications during the use of anticholinergics. In cases of mild anticholinergic toxicity, an alternative drug can usually be found that has less pronounced anticholinergic effects. The use of anticholinergics for the treatment of parkinsonian tremor should be avoided in patients older than 70 years or who have a history of dementia, hallucinations, severe constipation or urinary retention. Severe anticholinergic toxicity can be managed symptomatically with cooling blankets and the use of benzodiazepines to control seizures. Physostigmine effectively antagonises the toxic delirium associated with anticholinergic overdose.

1.2 Amantadine

Amantadine, originally developed as a treatment for influenza A, was fortuitously noted to ameliorate parkinsonian symptoms. Its effects in Parkinson's disease are believed to be mediated via the release of dopamine from nerve terminals,

Table I. Drugs with anticholinergic properties

Drug class	Individual drugs
Antiarrhythmics	Disopyramide, propafenone
Antiemetics	Cyclizine, meclozine (meclizine), scopolamine
Antihistamines	Brompheniramine, chlorphenamine (chlorpheniramine), cyproheptadine, diphenhydramine, hydroxyzine, triprolidine
Antiparkinsonians	Amantadine, trihexyphenidyl (benzhexol), benzatropine (benztropine), profenamine (ethopropazine), biperiden
Antispasmodics	Atropine, belladonna, hyoscyamine, dicycloverine (dicyclomine), flavoxate, scopolamine, isopropamide, oxybutynin, propantheline
Antiulcer drugs	Pirenzepine
Antiasthmatics	Atropine sulfate, ipratropium bromide
Anti-incontinence agents	Oxybutynin, propantheline bromide
Muscle relaxants	Baclofen, cyclobenzaprine, orphenadrine
Antipsychotics	Chlorpromazine, chlorprothixene, clozapine, loxapine, perphenazine, pimozide, mesoridazine, trifluoperazine, thioridazine
Tricyclic and related antidepressants	Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, protriptyline, nortriptyline, trimipramine

resulting in an increase in the availability of the neurotransmitter to activate postsynaptic dopamine receptors.[11] It also has some anticholinergic activity[12] and may function as an *N*-methyl-D-aspartate (NMDA) receptor agonist.[13]

Amantadine may cause a number of adverse dopaminergic and anticholinergic effects when taken as monotherapy. These consequences may be potentiated by concomitant use of other agents that have dopaminergic or anticholinergic properties. Additional potential adverse effects of amantadine include ankle swelling and peripheral oedema, the mechanism of which is unknown. Amantadine may cause livedo reticularis, a reversible mottled skin discoloration. Myoclonus has also been reported in patients taking the drug.[14]

Amantadine undergoes little systemic metabolism and normally 90% of a dose is excreted unchanged in the urine.[15] As such, this agent does not affect the metabolism of other drugs. There are rare reports of interactions between amantadine and diuretics. Toxic delirium has been reported in an elderly patient taking amantadine and cotrimoxazole (trimethoprim-sulfamethoxazole).[16] It was suggested that the trimethoprim component of cotrimoxazole competes with amantadine for renal secretion, allowing toxic concentrations of amantadine to accumulate. Both drugs by themselves can also cause mental confusion, especially in the elderly. Amantadine toxicity may result in agitation, hallucinations and ataxia, and has been reported when the drug is used with hydrochlorothiazide triamterene[17] or cyclopenthiazide potassium. In a case report, a patient receiving amantadine and hydrochlorothiazide triamterene showed a 50% rise in serum amantadine concentrations (from 156 to 243 μg/L) after taking the diuretic for a week.[15] Commonly prescribed thiazide diuretics may also reduce renal clearance of amantadine, allowing toxic concentrations to accumulate, a hazard of which clinicians should be aware.

1.3 Dopamine Receptor Agonists

A bewildering array of new dopaminergic agonists is now available to the clinician. In the US, bromocriptine, pergolide, pramipexole and ropinirole are approved for use; in Europe, cabergoline and lisuride are also available. Pramipexole and ropinirole, like bromocriptine and pergolide, act primarily through stimulation of striatal dopamine D_2 receptors, and are all nearly equipotent when given in optimal doses. Pramipexole and ropinirole have additional effects at the D_3 receptor, a pharmacologic profile of unclear significance. From a clinical perspective, the synthetic dopamine agonists are distinguished from each other by adverse effect profile, ease of titration and cost. All dopamine receptor agonists are suitable as monotherapy in early Parkinson's disease, or as adjuncts to levodopa treatment in more advanced disease. Lisuride is similar in most respects to pergolide. Cabergoline, due to its duration of effect, may eventually become an agent used primarily for the treatment of hyperprolactinaemia.

1.3.1 Bromocriptine

Bromocriptine is an ergot derivative that acts as an agonist at D_2 receptors and has weak antagonist activity at D_1 receptors. The drug also has weak affinity for α-adrenergic receptors and inhibits prolactin release from the anterior pituitary. Its effect in Parkinson's disease is attributed to its action at postsynaptic D_2 receptors in the striatum.

Like all dopaminergic agents, bromocriptine may cause hallucinosis or dyskinesias. Dopaminergic adverse effects may occur when bromocriptine is used as monotherapy or in combination with other dopamine agonists. Its α-adrenergic effect may lower blood pressure.

Bromocriptine, by virtue of being an ergot derivative, can directly cause headache, cerebral and peripheral vasospasm, cardiac arrhythmias and hypertension. There is no information regarding the incidence of these symptoms in patients who experience migraine headaches who would be expected to be more susceptible to the effects. These adverse effects may be potentiated in the presence of sympathomimetic agents.[18] Therefore, patients should be cautioned against the use of OTC medications containing sympathomimetics (e.g. amphetamine, ephedrine, isometheptine mucate, phenyl-

propanolamine and pseudoephedrine) while taking bromocriptine.

The most important potential drug interaction with bromocriptine occurs in the presence of macrolide antibacterials. It is suggested that these drugs inhibit the metabolism of bromocriptine by the liver, thus allowing toxic concentrations to accumulate. In a study involving healthy volunteers, the addition of erythromycin estolate 250 mg/day for 4 days altered the pharmacokinetics of a single 5mg dose of bromocriptine. Bromocriptine clearance was decreased by 70.6%, peak plasma concentrations were increased by 460% and the area under the plasma concentration-time curve was increased by 268%.[19] Thus, the combination of bromocriptine and macrolide antibacterials, including josamycin and erythromycin, can enhance the clinical effects[20] or toxicity of bromocriptine, or result in full-blown ergotism.[4]

It has been suggested that alcohol (ethanol) may induce an increase in sensitivity of dopamine receptors to bromocriptine, but this has not been systematically studied or evaluated in patients with Parkinson's disease. However, a case report has described 2 patients with acromegaly, but not Parkinson's disease, who were treated with bromocriptine and also consumed alcohol. Adverse effects occurred at lower dosages of bromocriptine when the patients drank alcohol. Conversely, abstaining from alcohol allowed higher dosages of bromocriptine to be used without adverse effects.[21] The action of bromocriptine can also be opposed by the oral antifungal agent griseofulvin, as reported in a patient with acromegaly.[22] The mechanism of this interaction is unknown.

In order to minimise orthostatic hypotension, therapy with bromocriptine is usually started with a test dose of 1.25mg at bedtime. This can then be switched to a morning dose after 3 days and the dosage gradually increased to a thrice daily schedule in 1.25 to 2.5mg increments every 3 to 7 days. This principle of building up to an efficacious dosage in small steps also helps avoid the dopaminergic complications of hallucinosis or psychosis. Hypotension may also be effectively antagonised by the α_1-agonist midodrine. Ergotism, should it develop in a patient taking bromocriptine in combination with sympathomimetics, may be treated in extreme cases using vasodilators, including sodium nitroprusside, and epidural blockade.[23]

1.3.2 Pergolide

Pergolide is a synthetic ergot derivative that acts as a potent agonist at D_2 receptors and a weak agonist at D_1 receptors. It exerts its antiparkinsonian effects by stimulating postsynaptic dopaminergic receptors in the striatum. Its dopamine agonist potency exceeds that of bromocriptine by about 10-fold on a milligram per milligram basis.

As an ergot derivative, pergolide may cause headache and the range of vascular effects described with bromocriptine (section 1.3.1). As a result of its dopamine receptor agonist properties, pergolide may induce dyskinesias, hallucinations, and psychosis. It may also cause hypotension in susceptible patients and should be administered with caution in patients already receiving antihypertensive medications.

Pergolide is 90% bound to plasma proteins[24] and should therefore be administered with caution in patients receiving other drugs known to affect protein binding. Thus, the potential for interaction exists with other protein-bound drugs such as aspirin (acetylsalicylic acid) and other anti-inflammatory drugs, probenecid, penicillins, sulphonamides, oral anticoagulants, methotrexate, phenytoin and valproic acid (sodium valproate). For example, an increase in dyskinesias in a patient taking both levodopa/carbidopa and pergolide has been reported after the addition of warfarin.[4]

As with bromocriptine, orthostatic hypotension may complicate initial therapy, but can be limited by using a slow dosage escalation schedule, beginning with a bedtime dose of 0.05mg. A gradual increase thereafter to an average daily dose of 3mg over 1 to 2 months helps avoid other potential adverse effects, which are similar to those of bromocriptine (see section 1.3.1).

1.3.3 Pramipexole

Pramipexole is a new non-ergot dopamine receptor agonist for treating Parkinson's disease that

was launched in 1997. Pramipexole is a D_2 receptor agonist that has additional agonist activity at D_3 receptor sites, located in the ventral striatum (nucleus accumbens) and olfactory tubercle.[25] The relevance of D_3 receptor binding in Parkinson's disease is unknown, but because the drug is not an ergot derivative, the incidence of adverse effects should be less than that associated with the earlier dopamine receptor agonists bromocriptine and pergolide. The efficacy of pramipexole is similar to that of bromocriptine and pergolide when given at an optimal and equivalent dosage.

There is little clinical experience to date with pramipexole, outside of pre-marketing clinical trials. Trials of pramipexole as monotherapy in early Parkinson's disease showed a significant symptomatic benefit as compared with placebo. In advanced Parkinson's disease, when added to levodopa, pramipexole was associated with improvements in motor performance, decreased disability and a reduction in wearing-off fluctuations. Pramipexole also enabled a reduction in the daily levodopa requirement.[26]

Pramipexole is secreted 90% unchanged in the urine. As such, patients with renal disease require lower dosages of the drug than those without renal disease. Pramipexole may potentiate the dopaminergic adverse effects of levodopa and other dopamine agonists when used concurrently.[27]

The most common adverse effects of pramipexole when given as a single agent are excessive drowsiness, nausea, dizziness, hallucinations, constipation and hypotension. When given with levodopa to patients with more advanced Parkinson's disease, pramipexole is associated with dyskinesias and hallucinations.[27] There is no information to date regarding specific pharmacological interactions between pramipexole and other medications.

1.3.4 Ropinirole

Ropinirole is the second new non-ergoline dopamine receptor agonist. It was launched in the US in 1997 for the treatment of Parkinson's disease.

The drug binds to post-synaptic dopamine receptors of the D_2 family, comprising D_2, D_3 and D_4 receptors. Its binding affinity for D_3 receptors exceeds that for D_2 and D_4 receptors, giving it a similar receptor binding profile to pramipexole. Unlike pergolide or bromocriptine, ropinirole has little activity at D_1 receptors. Its symptomatic effect in Parkinson's disease is attributed to D_2 receptor agonist effects at the receptors in the caudate and putamen. The therapeutic significance of D_3 receptor binding is unknown.[28]

Ropinirole is extensively metabolised by the liver to inactive metabolites. Its elimination half-life is 6 hours.[28]

Ropinirole is effective as monotherapy in early Parkinson's disease, or as an adjuvant agent in patients with advanced Parkinson's disease who are taking levodopa. In a multicentre, randomised, placebo-controlled clinical trial, ropinirole monotherapy for patients with mild Parkinson's disease improved motor scores and was well tolerated.[29] The mean daily dose of ropinirole in this study was approximately 15mg. In an unpublished comparison of ropinirole (mean daily dose 12mg) and bromocriptine (mean daily dose 24mg) in the treatment of early Parkinson's disease, ropinirole was more effective in reducing parkinsonian motor scores on the Unified Parkinson's Disease Rating Scale.[30] When added to levodopa in patients with advanced Parkinson's disease that was complicated by wearing-off fluctuations, ropinirole was associated in a mean reduction in 'off' time of 1 hour daily, and a reduction in levodopa daily dose requirement of about 20%.[31]

The most common adverse effect of ropinirole is nausea, occurring in as many as 50% of the patients who received the drug in 1 study,[28] but was rarely severe enough to warrant discontinuation. This adverse effect can be reduced by taking the medication with food. Dizziness and somnolence are also frequent. Other less common adverse effects include headache, syncope, oedema, fatigue, hallucinations and confusion.

When ropinirole is taken in tandem with levodopa, drug-induced adverse effects are common, but can also occur with ropinirole as monotherapy. Patients with liver disease or individuals taking concurrent medication that inhibits hepatic meta-

bolism might be susceptible to dopaminergic adverse effects of ropinirole, but this has not been reported.

1.4 Levodopa

Since its introduction in the 1960s, levodopa has been the mainstay of treatment for Parkinson's disease. Unlike dopamine itself, levodopa crosses the blood-brain barrier. It is then decarboxylated to dopamine and is released by presynaptic terminals in the striatum, where it replenishes the dopaminergic deficiency that is characteristic of Parkinson's disease. Given orally, levodopa is approximately 95% decarboxylated by mucosa amino acid decarboxylase to dopamine, which, as mentioned above, cannot cross the blood-brain barrier. The conversion of levodopa to dopamine requires pyridoxal-5-phosphate as a cofactor. When dietary pyridoxine (vitamin B_6) levels are high, this peripheral decarboxylation of levodopa is increased. In early studies, pyridoxine was shown to block the effects of levodopa.[32] The effect of pyridoxine is abolished in the presence of a peripheral decarboxylase inhibitor such as carbidopa or benserazide. The ingestion of pyridoxine has no effect in patients taking combined carbidopa and levodopa or benserazide and levodopa, and no restriction on pyridoxine intake is needed.

The absorption of levodopa occurs primarily in the duodenum and jejunum by means of an amino acid carrier-mediated transport system. Factors that decrease gastric emptying, such as food intake, gastric acidity and anticholinergic medication, can delay the delivery of levodopa to the small intestine, allowing more time for peripheral decarboxylation. Protein intake may interfere with levodopa treatment because neutral amino acids will compete with levodopa for transport across the gut and the blood-brain barrier. The levodopa metabolite 3-*O*-methyldopa (3-OMD) may also potentially compete with levodopa for transport across these membranes (see section 1.6).[33]

Antacids that contain magnesium, such as milk of magnesium, accelerate gastric emptying and can decrease the gastric metabolism of levodopa, thus increasing its bioavailability. Excessive neutralisation of the gastric acid environment may however decrease tablet dissolution, and reduce the bioavailability of levodopa.[34] In practice, therefore, it is difficult to predict the effect of antacids on the metabolism of levodopa, and both increased[10,35] and decreased[36] bioavailability have been reported. Animal experiments[37] and human studies have demonstrated that ferrous sulfate can reduce the bioavailability of levodopa.[38,39] The anti-nausea agent metoclopramide, while inducing parkinsonism (see section 2.1), can increase the bioavailability of levodopa,[40] although the combined outcome of these effects is uncertain.

Certain antihypertensive agents may interact with levodopa. Methyldopa may cause a reversible parkinsonian syndrome,[41-43] by producing α-methyldopamine, a partial agonist that competes with dopamine for receptor sites.[44] Combined use of levodopa and methyldopa may have an additive effect in lowering blood pressure.[45] Clonidine has been reported to worsen the rigidity and akinesia of Parkinson's disease.[46] Reserpine, an antihypertensive agent that depletes brain monoamines, may induce a worsening of Parkinson's disease, both in the presence or absence of levodopa.[47] Tetrabenazine may produce the same effect by a similar mechanism.

Depression is common in patients with Parkinson's disease. Fortunately, most antidepressants can be given in conjunction with levodopa, although amoxapine, which can induce reversible parkinsonism via dopaminergic blockade, should be avoided in patients with Parkinson's disease.[48]

Monoamine oxidase inhibitors (MAOIs) are specifically contraindicated in patients receiving levodopa or dopamine agonists. MAOIs increase the circulating levels of dopamine and noradrenaline (norepinephrine), causing excessive stimulation of cardiovascular α-adrenoreceptors. These agents, in combination with levodopa, may produce a life-threatening hypertensive crisis (see section 2.5.1). Patients should not receive levodopa while they are on MAOI therapy, or for a period of 2 to 3 weeks after their withdrawal. Selegiline, with

its relative selectivity for MAO-B, is unlikely to interact in this manner with levodopa when given at a therapeutic dosage (10 mg/day).[49]

Rare hypertensive crises of unknown mechanism have been reported when levodopa and tricyclic antidepressants have been coadministered.[50] Due to their anticholinergic adverse effects, tricyclics can slow gastric emptying, thereby increasing the gastric metabolism of levodopa and reducing its bioavailability.[51]

Other interactions between levodopa and additional agents have been reported, although the combination of these medications is rarely encountered. Dacarbazine, used in the treatment of malignant melanoma, may oppose the effect of levodopa via competition for transport across the blood-brain barrier;[52] increasing the dosage of levodopa may counter this effect.[53] The macrolide antibacterial spiramycin forms a non-absorbable complex with carbidopa, thus decreasing the bioavailability of levodopa.[54] Penicillamine, a chelating agent used in Wilson's disease, heavy metal intoxication and rheumatoid arthritis, has been described as increasing plasma levodopa concentrations by aiding intestinal absorption of the drug.[55]

Levodopa replacement may be associated with reversible adverse effects that can limit treatment. Gastrointestinal complaints are among the most common adverse effects of levodopa/carbidopa therapy. Nausea, anorexia and vomiting are often reported, especially during the initiation of therapy. These effects are caused, in large part, by dopamine activation of the emesis centre, the area postrema which lies outside of the blood-brain barrier. Peripheral decarboxylase inhibitors limit the peripheral formation of dopamine, a strategy that is highly effective in reducing nausea and emesis. These adverse effects can also be limited by: (i) having patients take levodopa/carbidopa with meals; (ii) increasing the dosage gradually until tolerance develops; (iii) supplying additional carbidopa or benserazide; (iv) utilising the controlled release formulation of levodopa/carbidopa; or (v) adding the peripheral dopamine receptor antagonist domperidone.

CNS adverse effects of levodopa are common in patients with Parkinson's disease and may be triggered by an underlying susceptibility in patients with concomitant dementia, even of mild degree. Confusion, drowsiness, hypersomnolence, behavioural changes, vivid dreams, nightmares or frank hallucinosis may follow levodopa treatment. The drug can also induce involuntary choreic movements, termed dyskinesias, in patients with parkinsonism. These movements are often mild, but may increase in proportion to the dosage of levodopa, necessitating a dosage reduction.

Other adverse effects of levodopa/carbidopa include postural hypotension and cardiac arrhythmias. Postural hypotension can be severe enough to cause syncope. Patients taking concurrent antihypertensives, including the agents described above, pose a special risk in this regard. Reducing the levodopa dosage, increasing fluid and salt intake, the use of antigravity stockings and the occasional administration of the mineralocorticoid fludrocortisone or the peripheral α_1-agonist midodrine may be indicated. Dopaminergic stimulation via use of levodopa may induce cardiac tachyarrhythmias in susceptible patients. β-Blocking drugs have been advocated to prevent this adverse effect.[56] The tremor of Parkinson's disease may also be reduced in some patients taking β-blockers.[57] Dopaminergic stimulation via use of levodopa may induce cardiac tachyarrhythmias in susceptible patients. β-Blocking drugs have been advocated to prevent this adverse effect.[56]

Within several years of beginning treatment with levodopa (or a dopamine receptor agonist), 50% of patients develop unwanted complications of therapy, including wearing-off motor fluctuations and dyskinesias.[58] These troublesome problems may limit the treatment of Parkinson's disease, and often herald a period of increasing disability. Increasing the dosages of antiparkinsonian medication, including levodopa, may overcome this problem, but may also escalate the potential for drug interactions and adverse events. A recent study also indicated a favourable effect of β-blockers on levodopa-induced dyskinesias,[59]

and study of 5 patients being treated with levodopa showed that phenytoin relieved levodopa-induced dyskinesias, but that the beneficial effects of levodopa were also diminished.[60] Many pharmacological adjustments can improve the complications of motor fluctuations and dyskinesias, including changes in the drug dosage and intervals, using combined therapy with regular and long-acting levodopa or combinations of dopamine receptor agonists, liquid levodopa,[61-63] addition of clozapine,[64] and alterations in protein intake. New classes of antiparkinsonian agents, including the COMT inhibitors and glutamate antagonists, are being developed to reduce these complications.

1.5 Selegiline (Deprenyl)

Selegiline is a synthetic, selective, irreversible inhibitor of MAO-B, the main catalytic enzyme for dopamine. Complete recovery of MAO-B activity does not occur for several weeks after selegiline treatment is terminated.

Selegiline was first reported as a useful adjunct to levodopa in patients with advanced Parkinson's disease that was complicated by motor fluctuations.[65] The compound has been evaluated as a possible neuroprotective agent in Parkinson's disease, based on the hypothesis that inhibition of MAO-B may reduce the formation of peroxides and free radical species generated by the oxidation of dopamine. Selegiline has been reported to delay the need for levodopa therapy when given to patients with mild, early Parkinson's disease, which is consistent with its putative action as a neuroprotective antioxidant.[66] However, the direct symptomatic action of selegiline confounds the detection of a neuroprotective effect.[54]

Selegiline does not significantly alter the distribution or elimination of levodopa from plasma,[67] but may boost the effect of endogenous dopamine stores, giving a mild symptomatic effect in patients with Parkinson's disease.[68] Patients taking selegiline may experience an exacerbation of levodopa-induced adverse effects, such as dyskinesias. These effects may be mitigated by reducing the dosage of levodopa by 10 to 30%. The most frequently reported adverse effects of selegiline are neurobehavioural disturbances such as nightmares, insomnia, confusion and hallucinations. At dosages of less than 10 mg/day, selegiline is not associated with the catecholaminergic 'cheese reaction' that may occur with MAO-A or combined MAO-A and MAO-B inhibitors. However, at dosages exceeding 30 mg/day, selegiline loses its selectivity for MAO-B and has the potential to cause a hypertensive crisis if excessive dietary tyramine is consumed, or it is taken with sympathomimetic agents.

A syndrome resembling the serotonin syndrome has been reported when selegiline was taken in combination with the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor (SSRI) fluoxetine.[69] This syndrome is characterised by CNS irritability, hypertonia, shivering, myoclonus and altered mental status (see section 2.5.2).[70,71] Ataxia has also been reported in a woman with Parkinson's disease who was receiving multiple medications, including fluoxetine and selegiline.[72] A pseudophaeochromocytoma syndrome developed in a patient being treated with levodopa, carbidopa, bromocriptine, domperidone and selegiline when fluoxetine was added.[73] In contrast to these isolated reports, however, in a series of 23 patients, administration of fluoxetine 5 to 40 mg/day and selegiline 5 to 10 mg/day did not result in any cases of the serotonin syndrome.[74] In this series, the adverse effects of combined selegiline-fluoxetine treatment included nervousness, dizziness, increased tremor, nausea and, in 4 demented patients, confusion and hallucinations. The incidence of serotonin syndrome with selegiline is exceedingly low, but it is nonetheless prudent for clinicians to be aware of this potential complication. In theory, similar interactions between selegiline and other SSRIs, including paroxetine, sertraline or fluvoxamine, or the mixed noradrenaline-serotonin reuptake inhibitor venlafaxine, could occur, but have not been reported (see section 2.5.2).

A 'central excitatory syndrome' occasionally occurs when a nonselective MAOI is used concomitantly with the opioid analgesic pethidine (meperidine).[75] The clinical manifestations in-

clude delirium, excitation, hyperthermia, respiratory depression and rigidity. A similar excitatory reaction was reported in a patient who was receiving selegiline, pergolide, levodopa/carbidopa, imipramine and desipramine,[76] which resolved when selegiline was discontinued. In practice, it is prudent to avoid the combination of selegiline and pethidine, and many neurologists discontinue selegiline several weeks before patients are scheduled to undergo elective surgery. No important pharmacological interactions have been reported between selegiline and other opioids, including codeine, dextropropoxyphene (propoxyphene) or morphine.

Hypertensive crises and disseminated intravascular coagulation have been reported when tricyclic antidepressants were used together with MAOIs.[77,78] Theoretically, such an interaction is also possible with selegiline in quantities exceeding 10 mg/day, but this dosage is not indicated in the treatment of Parkinson's disease.

1.6 Catechol-*O*-Methyltransferase Inhibitors

COMT inhibitors are new additions to the therapeutic approach to Parkinson's disease. Two agents, entacapone and tolcapone, have recently been approved for the treatment of Parkinson's disease in some countries. These nitrocatechol compounds bind to the substrate binding site of COMT in a noncompetitive manner, causing prolonged inhibition of COMT activity. COMT inhibitors prevent the normal methylation of levodopa to its metabolite 3-OMD, a reaction that diverts a portion of the levodopa from conversion to dopamine. By limiting this 'metabolic loss' of levodopa to 3-OMD, COMT inhibitors increase the availability of levodopa for dopamine production. COMT also metabolises dopamine to 3-methoxytyramine (3-MT) and the dopamine metabolite dihydroxyphenylacetic acid (DOPAC) to homovanillic acid (HVA) [see fig. 1].[79]

Tolcapone is a selective, reversible, peripherally and centrally active COMT inhibitor. Entacapone is a highly selective, reversible COMT inhibitor that acts in the periphery to reduce COMT activity in the gut, erythrocytes and liver. Brain COMT is only slightly and transiently reduced, so for clinical purposes, entacapone, unlike tolcapone, is not considered centrally active.

COMT inhibitors taken orally in combination with levodopa and carbidopa reduce peripheral 3-OMD formation from levodopa, enabling more levodopa to enter the brain. Tolcapone also enters the brain directly, where it increases whole brain concentrations of levodopa and dopamine, and reduces the levels of the metabolites 3-OMD, 3-MT and HVA. As a result, serum and brain levodopa concentrations, and dopamine and DOPAC levels all increase after an oral dose of a COMT inhibitor.[80] Positron emission tomography (PET) studies demonstrate that entacapone can increase the striatal uptake of fluorodopa. COMT inhibitors increase the bioavailability and half-life of levodopa, and therefore increase and prolong its clinical effect.[81]

Administration of entacapone or tolcapone is associated with a high incidence of disabling dyskinesias, often necessitating a reduction in levodopa dosage. Other potential adverse effects of COMT inhibitors include diarrhoea, nausea, dizziness, urine discoloration, and prolongation and increase of levodopa-induced adverse effects, including dyskinesias.

Carbidopa and benserazide are also substrates for COMT, and the action of these decarboxylase inhibitors may be prolonged by COMT inhibitors. COMT inhibition may allow more benserazide to enter the CNS where it can inhibit the conversion of levodopa to dopamine.[82] In addition, COMT inhibitors have a potential interaction with other drugs that are substrates for COMT (see table II).[83]

Because COMT inhibitors are a new class of drug that is still under investigation, more experience is needed before the role that they have in the therapeutic repertoire for Parkinson's disease can be determined.

1.7 Clozapine

Until the advent of clozapine, the only effective treatment for psychosis or dopaminergic-induced hallucinations in patients with Parkinson's disease

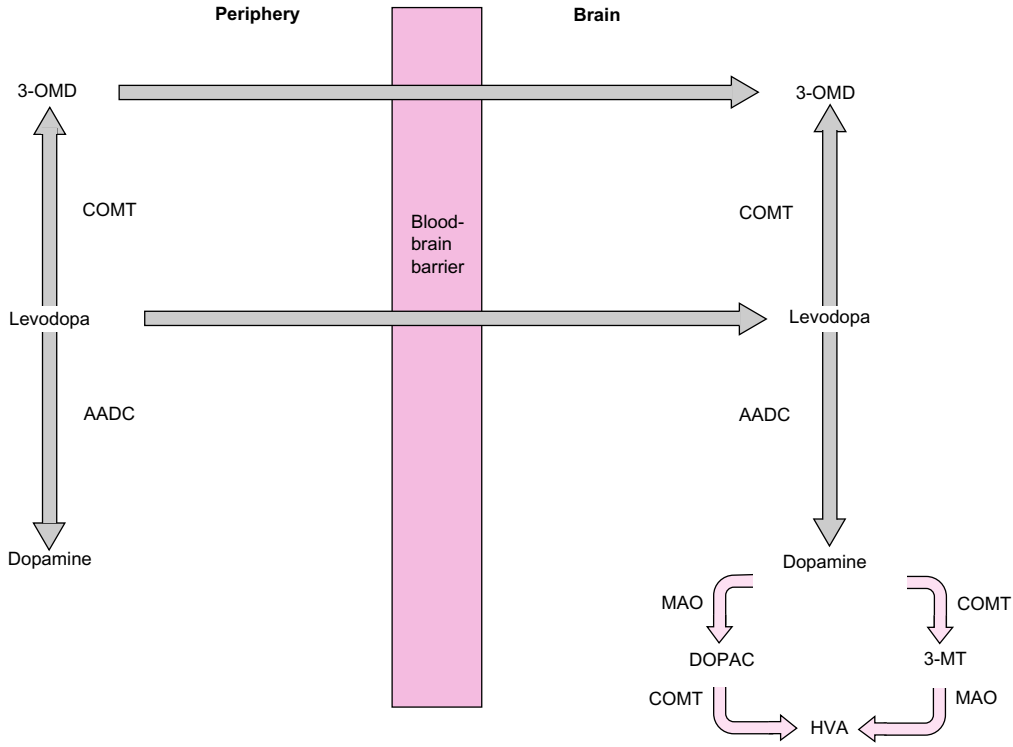

Fig. 1. Metabolism of levodopa. *Abbreviations:* AADC = aromatic amino acid decarboxylase; COMT = catechol-*O*-methyltransferase; DOPAC = dihydroxyphenylacetic acid; HVA = homovanillic acid; MAO = monoamine oxidase; 3-MT = 3-methoxytyramine; 3-OMD = 3-*O*-methyldopa.

was to lower the medication dosage or add a dopamine receptor blocking agent. However, these options also worsen the symptoms of Parkinson's disease.

Clozapine, a tricyclic dibenzodiazepine derivative, is considered to be an 'atypical' antipsychotic agent because it does not cause parkinsonism or tardive dyskinesia. Its profile of receptor interactions includes D_4 receptor antagonism, serotonin 5-HT_2 receptor antagonism, α_2-receptor antagonism and partial cholinergic M_1 agonist activity. It is thus especially useful in the treatment of psychosis and drug-induced hallucinations in patients with Parkinson's disease.[84] In addition, it appears to have direct antiparkinsonian effects, such as a reduction in tremor.[85] As such, clozapine has become a valuable addition to the treatment of Parkinson's disease and its complications.

The most common potential adverse effects of clozapine include excess sedation and hypotension. The sedative effect can be reduced by administering a low dose of clozapine, such as one quarter of a 25mg tablet, at bedtime. This dose is effective for many patients with Parkinson's disease, and provides the additional benefit of an hypnotic for individuals with insomnia or sleep-wake reversal. The hypotensive effect of clozapine, related to α_2-receptor antagonism, may be enhanced in patients with Parkinson's disease and is potentiated by antihypertensives or dopamine receptor agonists, such as pergolide. Eliminating concomitant antihypertensives, increasing fluid and salt intake, or using compression stocking may solve this problem. In severe hypotension, the addition of midodrine or fludrocortisone may be necessary. The major disadvantage of clozapine is the risk of

Table II. Substrates for catechol-*O*-methyltransferase (COMT)

Drug class	Drug
Antiparkinsonian drugs	Apomorphine, benserazide, carbidopa, dopamine
Cardiovascular drugs	α-Methyldopa, dobutamine, epinephrine (adrenaline), isoprenaline (isoproterenol), norepinephrine (noradrenaline)
Miscellaneous	Rimiterol, 2-hydroxylated estrogens

neutropenia, which necessitates weekly monitoring of the white blood cell count.

Additional drug interactions have also been reported with clozapine. Serum clozapine concentrations doubled within 2 weeks of withdrawing coadministered carbamazepine in 2 patients.[86] The neuroleptic malignant syndrome was reported in a man being treated with carbamazepine when clozapine was substituted for lithium.[87] Phenytoin, when given to 2 patients who were also receiving clozapine,was associated with a reduction in serum clozapine concentrations and worsened psychosis.[88]

Interactions between clozapine and benzodiazepines have been described. Hypotension, respiratory depression and coma[89] as well as sedation, ataxia and hypersalivation[90] have all been reported. In 1 patient, cimetidine caused an increase in serum clozapine concentrations and clozapine toxicity, manifested by diaphoresis, vomiting, dizziness and orthostatic hypotension.[91] This was likely to have been due to the effects of cimetidine on liver metabolism via the inhibition of cytochrome P450 enzymes. Myoclonus was reported in a man receiving lithium following the addition of clozapine.[92] Neuroleptic malignant syndrome has also been reported in patients receiving this drug combination.[93]

Olanzapine, a new thienobenzodiazepine antipsychotic, appears to be effective for psychosis in patients with Parkinson's disease without worsening parkinsonism in most patients.[94] This agent does not require weekly blood monitoring, which represents a distinct advantage compared with clozapine. Risperidone, another recently launched antipsychotic agent, was reported to improve psychosis in patients with Parkinson's disease, but causes significant worsening of parkinsonian symptoms.[95,96]

2. Management Issues of Special Problems Associated with Pharmacotherapies for Parkinson's Disease

Descriptions of antiparkinsonian medications and their adverse effects and specific drug interactions have been outlined in section 1. In this section, the management of problems that have specific pharmacological implications in Parkinson's disease are described.

2.1 Drug-Induced Parkinsonism

Several classes of drugs can have direct adverse effects on the symptoms of Parkinson's disease. It is important for the clinician to be aware of the different parkinsonism-inducing agents a patient may be taking, especially if an antiparkinsonian medication appears to be less effective than expected. In current clinical practice, a patient may consult a variety of specialists, and the addition of a new medication that interacts with antiparkinsonian agents may not be recognised. All physicians caring for individuals with Parkinson's disease are obliged to list all the medications each patient is taking, including OTC remedies, at each visit.

All dopamine blocking agents or catecholamine-depleting substances, including conventional antipsychotic agents (see table III), may induce a state of parkinsonism, exacerbate the symptoms of Parkinson's disease and counter the effects of levodopa and other antiparkinsonian agents. The incidence of drug-induced parkinsonism in patients receiving antipsychotics is as high as 61%, according to 1 study,[97] and occurs increasingly with advanced age,[98] in parallel with the incidence of Parkinson's disease.

Although antipsychotics are the most common cause of drug-induced parkinsonism, several other offenders are listed in table IV. Antiemetics such as prochlorperazine and trifluoperazine can have a similar effect via blockade of dopamine receptors.

Table III. Antipsychotics that can induce parkinsonism

Class	Drug
Phenothiazine	Chlorpromazine
	Trifluoperazine
	Thioridazine
	Mesoridazine
	Trifluoperazine
	Perphenazine
	Fluphenazine
	Pimozide
	Acetophenazine
Thioxanthine	Chlorprothixene
	Thiothixene
Butyrophenone	Haloperidol
	Droperidol
Dibenzazepine	Loxapine
Indolone	Molindone
Pyrimidinone	Risperidone
Substituted benzamide	Tiapride
	Sulpiride
	Clebopride
	Remoxipride

Metoclopramide and clebopride, which possess central D_2 receptor antagonistic activity, can also cause a reversible parkinsonian syndrome.[107,108]

Drug-induced parkinsonism may occur with calcium antagonists that are commonly used in the treatment of hypertension and coronary artery disease. These drugs may possess a direct dopamine receptor antagonist effect, or decrease dopaminergic transmission by reducing the level of intracellular calcium that is required for dopamine release.[109] Agents most frequently reported to produce clinical parkinsonism are flunarizine and cinnarizine, piperazine derivatives that have central D_2 receptor blocking activity.[110] Parkinsonism has been reported as a result of treatment with verapamil[111] and diltiazem.[112] The antiarrhythmic agent amiodarone has also been reported to induce parkinsonism.[113]

The antidepressant-anxiolytic agent buspirone is a serotonin receptor agonist, but also possesses mixed agonist and antagonist effects at dopamine receptors in the striatal dopaminergic system.[114] Buspirone may induce a variety of involuntary movements, but cases of drug-induced parkinsonism have not been reported.[115] Valproic acid–induced reversible parkinsonism has been described in a child.[116]

2.2 Nausea and Constipation

Nausea and constipation are among the most frequent complaints of patients taking antiparkinsonian medications, alone or in combination. Often, the administration of levodopa or a dopamine receptor agonist with meals or the addition of pure carbidopa can prevent nausea.

Most antiemetics have central as well as peripheral dopamine receptor antagonist effects, including the widely prescribed agents metoclopramide and prochlorperazine. Domperidone, a peripheral dopamine receptor antagonist, has been used to combat the nausea caused by bromocriptine or levodopa. It acts on dopamine receptors in the gastric wall, with minimal penetration of the blood-brain barrier. Hence, it has significantly fewer extrapyramidal adverse effects than metoclopramide. In addition, it may even increase the bioavailability of levodopa.[117] Domperidone can increase prolactin levels, sometimes causing galactorrhoea, an effect opposite to that of bromocriptine.[118]

Cisapride can help relieve the chronic constipation that is a feature of Parkinson's disease itself or the result of anticholinergic medications. It acts by facilitating the release of acetylcholine from the myenteric plexus.

Table IV. Drugs for medical indications that have potential dopamine receptor blocking effects

Drug class	Drug
Antiemetics and cough suppressants	Prochlorperazine, promethazine, chlorpromazine, triethylperazine, trifluoperazine, metoclopramide
Antiarrhythmic	Amiodarone
Antihypertensives	Methyldopa, reserpine
Calcium antagonists	Amlodipine,[99] flunarizine, cinnarizine, diltiazem, verapamil
Tricyclic antidepressant	Amoxapine
Miscellaneous agents	Disulfiram,[100] fluoxetine, lithium,[101] manganese,[102] pethidine (meperidine),[103] phenelzine,[104] tacrine,[105] vaccines,[106] valproic acid (sodium valproate)

2.3 Psychosis in Parkinson's Disease

Psychosis is a common problem in patients with Parkinson's disease, occurring either as a result of the disease, an adverse effect of pharmacotherapy or a drug interaction.[119] Vivid dreams, visual hallucinations, hypomania and psychosis represent a spectrum of adverse symptoms that may be caused by antiparkinsonian medications. A paranoid delusion involving the spouse or main caregiver is a common form of psychosis in this setting.[120]

For patients with psychosis, dopaminergic medications should be reduced, starting with the drug thought to be the least helpful in treating the motor symptoms in a given patient. If this is unsuccessful in relieving the psychotic symptoms, or if motor function deteriorates, an atypical antipsychotic that does not cause parkinsonism may be prescribed, i.e. clozapine or olanzapine (see section 1.7). Ondansetron, a serotonin 5-HT_3 receptor antagonist used to reduce chemotherapy-related nausea, has also been reported to be useful in controlling drug-induced psychosis in patients with Parkinson's disease.[121]

2.4 Surgery in Patients with Parkinson's Disease

Patients with Parkinson's disease may undergo surgery as therapy for the disease itself or for concomitant illness. Successful perioperative management and anaesthesia requires knowledge of potential drug interactions.

Perioperative concerns in patients with Parkinson's disease include autonomic dysfunction, such as hypotension and disturbances in temperature regulation, pharyngeal dysfunction that increases the susceptibility for aspiration, pulmonary impairment due to chest wall immobility, and the potential complications of immobility and prolonged bedrest, such as deep vein thromboses and decubitus ulcers.[122] These issues are influenced by the antiparkinsonian treatment given during the perioperative period. It is usually important to resume the medications as soon as possible following surgery, via a feeding tube if necessary, so that patients can quickly be mobilised.

The sudden withdrawal of dopaminergic agonists during the perioperative period may, in theory, precipitate a neuroleptic malignant syndrome in patients receiving long term levodopa or dopamine agonists. This potentially severe complication should be managed with supportive measures including antipyretics, cooling blankets, intravenous hydration and respiratory support. Dantrolene can reduce rigidity and help lower fever.[123] Antiparkinsonian medications should be resumed as soon as possible.

The risk of postoperative confusion and hallucinations is higher in patients with Parkinson's disease than in those without the disease;[124] requiring careful vigilance and the judicious use of sedation and other measures.

Anaesthetic agents such as halothane are usually avoided in patients taking levodopa, since this combination may be associated with cardiac arrhythmias.[125] An acute dystonic reaction has been reported with alfentanil in a patient with untreated Parkinson's disease.[126] Morphine is preferred to pethidine in the treatment of postoperative pain if the patient has recently taken selegiline (see section 1.5).

2.5 Severe Drug Interactions

2.5.1 Hypertensive Crisis

A hypertensive crisis may be caused by an adverse interaction between high dosages of selegiline and dopaminergic or sympathomimetic agents. The condition is characterised by severe hypertension [systolic blood pressure (BP) ≥210mm Hg or diastolic BP ≥120mm Hg] with fulminant arteriopathy, associated with endothelial injury, intimal thickening and arteriolar occlusion.[127] Systemic complications include encephalopathy, stroke, renal failure and aortic dissection. Untreated malignant hypertension may become rapidly fatal and requires inpatient admission and emergency treatment.

The initial aim of therapy is to reduce diastolic BP, and sodium nitroprusside (0.25 to 8.0 μg/kg/min

Table V. Summary of clinically significant interactions and adverse effects associated with agents used in the management of Parkinson's disease

Antiparkinsonian drug	Potential adverse effects	Interacting drug	Interaction
Anticholinergics	Dry mouth, constipation, urinary retention, confusion	Levodopa	Reduced bioavailability of levodopa resulting in dementia, delirium and hallucinations
Amantadine	Dry mouth, constipation, urinary retention, livedo reticularis	Thiazide diuretics	Amantadine toxicity characterised by toxic delirium
		Cotrimoxazole (trimethoprim-sulfamethoxazole)	Amantadine toxicity characterised by toxic delirium
Bromocriptine	Headache, ankle oedema, livedo reticularis, cardiac arrhythmias	Sympathomimetics	Hypertension, tachycardia, cerebral vasospasm
		Macrolide antibacterials	Bromocriptine toxicity characterised by toxic delirium
Pergolide	Headache, syncope	Highly protein-bound drugs, e.g. aspirin (acetylsalicylic acid), warfarin, valproic acid (sodium valproate), phenytoin, sulphonamides	Competition for protein-binding sites resulting in toxic concentrations of either or both drugs
		Antihypertensives	Hypotension in susceptible patients
Levodopa	Nausea, vomiting, hypotension, somnolence, dyskinesias, hallucinations[a]	Antacids, spiramycin, anticholinergics	Reduced bioavailability of levodopa
		Domperidone	Reduced nausea, possibly increased bioavailability of levodopa
		Dopamine receptor–blocking antipsychotics	Exacerbation of parkinsonism, opposition of the action of levodopa and other dopamine agonists
		Methyldopa, clonidine, reserpine, tetrabenazine	Exacerbation of parkinsonism (see table IV)
		Non-selective MAO inhibitors or MAO-A inhibitors	Hypertensive crisis
		COMT inhibitors	Prolonged dyskinesias
		Selegiline (deprenyl), pergolide, amantadine, bromocriptine	Reduced requirement for levodopa can result in levodopa toxicity
Selegiline	Insomnia, agitation, jitteriness	Fluoxetine	Serotonin syndrome
		Tricyclic antidepressants	Hypertensive crisis (selegiline >30 mg/day)
Clozapine	Sedation, hypotension, seizures, agranulocytosis	Carbamazepine, lithium	Neuroleptic malignant syndrome
		Benzodiazepines	Hypotension, respiratory depression, coma
		Cimetidine	Clozapine toxicity characterised by orthostatic hypotension and nausea

a All the adverse effects listed for levodopa can also be seen with direct dopamine receptor agonists.

Abbreviations: COMT = catechol-*O*-methyltransferase; MAO = monoamine oxidase.

intravenously) is the agent of choice. Nitroglycerin (glyceryl trinitrate; 5 µg/min intravenously), trimetaphan (0.5 mg/min intravenously) and diazoxide (50mg every 5 to 10 minutes, up to 600mg) are also used. Other agents are required for longer term control of blood pressure, including enalaprilat (1.25mg every 6 hours intravenously), hydralazine (5 to 10mg every 20 minutes for 3 doses) and la-

betalol (20 to 80mg every 10 minutes, up to 300mg). These agents can be switched to their oral form once the hypertensive crisis is over.

2.5.2 Serotonin Syndrome

The serotonin syndrome is a symptom complex of confusion, agitation, rigidity, myoclonus and autonomic hyperactivity that may occur when serotonergic agents are given alone or in combination with monoamine oxidase inhibitors.[128] The syndrome may result from an interaction between high dosages of selegiline and serotonin reuptake inhibitors, but does not occur with the typical daily dose of selegiline that is used in Parkinson's disease (10mg).

Most cases of the serotonin syndrome are mild and respond to withdrawal of serotonergic drugs and general supportive care.[129] Management includes control of hyper-reflexia and myoclonus with benzodiazepines, and reduction of fever with paracetamol (acetaminophen). Patients with severe hyperthermia [>41°C (>105°F)] require aggressive cooling measures, including external cooling, muscular paralysis and intubation. Propranolol[130] and cyproheptadine[131] have been found to be useful in this setting.

3. Conclusions

Patients with Parkinson's disease are often treated using a combination of medications. In addition, many patients receive concurrent treatment for coexisting medical or psychiatric problems. The resulting polypharmacy carries a risk of drug interactions and adverse effects, many of which have been described in this review and are summarised in table V.

It is important that clinicians be aware of the more common drug interactions in order to use the available agents to maximum advantage for their patients with Parkinson's disease, while avoiding adverse effects. Given the wide array of antiparkinsonian agents, and the many additional pharmaceuticals for other conditions a patient may encounter, the number of reported interactions is surprisingly few. To date, most clinically significant interactions have been described in single case reports and are based on clinical observations rather than direct pharmacological measurements. Nonetheless, the potential for adverse effects and interactions always exists in patients with Parkinson's disease, and the clinician must be vigilant in drug monitoring.

With the addition of more agents for Parkinson's disease, including newer selective dopamine receptor agonists, new antioxidants, inhibitors of glutamate release and glutamate receptor antagonists, this area of therapeutics will become more complex, and the potential for drug interactions and adverse reactions will only increase.

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