rhoea. There appear to be no important differences in the efficacy of antimuscarinics for Parkinson's disease but some patients may tolerate one drug better than another. Those commonly used for Parkinson's disease include *benzatropine*, *orphenadrine*, *procyclidine*, and *trihexyphenidyl*.

- *Amantadine* is a weak dopamine agonist with some antimuscarinic activity although its activity as an antagonist of *N*-methyl-D-aspartate may also have a beneficial effect in Parkinson's disease. It has mild antiparkinsonian effects compared with levodopa but is relatively free from adverse effects. It can improve bradykinesia as well as tremor and rigidity but only a small proportion of patients derive much benefit. It is used similarly to antimuscarinics in early disease when symptoms are mild, but tolerance to its effects can occur rapidly.

Choice and implementation of drug treatment. If symptoms are mild, drug therapy may not be required in the early stages of the disease. When symptoms become troublesome but are still relatively mild *amantadine* or an *antimuscarinic* may be started; antimuscarinics are useful when tremor predominates but are generally more suitable for younger patients and in drug-induced rather than idiopathic parkinsonism. Some have begun treatment with *selegiline* immediately, but there have been doubts over whether it has a neuroprotective effect, as postulated, and also over long-term safety. There is no consensus on when to start dopaminergic treatment or whether to begin with *levodopa* or a *dopamine agonist*. For most patients treatment with levodopa eventually becomes necessary, but many neurologists delay initial treatment with levodopa because of the increased risk of motor complications. New patients, especially younger patients, therefore often begin treatment with a dopamine agonist, with levodopa reserved for the elderly, the frail, or those with intercurrent illness or more severe symptoms.

When levodopa does become necessary, the usual practice is to start with small doses, together with a peripheral dopa-decarboxylase inhibitor, and increase slowly to a dose which reduces disability to an acceptable level. Variations in response and diminishing effectiveness over the years necessitate careful adjustment of the size and form of the dose and the dosage schedule.

Complications of treatment. Fluctuations in mobility have been reported in more than half of patients on levodopa after 5 years of therapy. They generally proceed through predictable **'end-of-dose'** deterioration to the **'on-off'** phenomenon with marked very sudden swings from mobility to immobility. The cause of the fluctuations is not known, but multiple factors including desensitisation of dopamine receptors, interference with the response to dopamine by other levodopa metabolites such as 3-*O*-methyldopa, fluctuating plasma concentrations, and erratic transport of levodopa from blood to the brain have been suggested. It appears that as the disease progresses the capacity of the nigrostriatal dopaminergic system to synthesise and store dopamine, and to act as a buffer in maintaining dopamine brain concentrations, declines. Dopamine concentrations therefore become more dependent on levodopa dosage and the pattern of response will come to reflect more closely the rise and fall in levodopa concentrations. Eventually the effect of various factors that produce even small changes in plasma concentrations of levodopa will progressively become more pronounced.

Approaches to the management of 'end-of-dose' fluctuations include more frequent but smaller doses and the use of modified-release preparations. Addition of selegiline or partial replacement of levodopa by a dopamine agonist with a more prolonged action may also be tried.

Various attempts have been made to overcome the 'on-off' phenomenon. Those speculating that long-term treatment results in altered dopamine receptor sensitivity have used controlled withdrawal of levodopa for short periods ('drug holidays') but it is a dangerous procedure of doubtful value and no longer recommended.

Others have linked the 'on-off' phenomenon to variable plasma concentrations although, since transfer of levodopa into the brain involves active transport mechanisms, concentrations in plasma may not necessarily reflect those in the brain. Continuous intraduodenal or intravenous infusion of levodopa has been shown to reduce fluctuations in mobility, which suggests that dopamine receptors are still sensitive, although this is not practical for day-to-day management (but see below). However, there is evidence that some patients may benefit from modified-release formulations of levodopa with a peripheral dopa-decarboxylase or COMT inhibitor. As levodopa competes with amino acids for uptake into the brain, attempts to lessen fluctuations in dopamine brain concentrations have included taking levodopa on an empty stomach and also delaying most of a day's protein consumption until the evening. Addition of entacapone, rasagiline, selegiline, or a dopamine agonist may also help to reduce 'on-off' phenomena. If fluctuations remain a problem subcutaneous apomorphine is often effective. In some countries a gel formulation of levodopa with carbidopa is available for continuous infusion by an ambulatory pump into the duodenum when other available combination therapy has not been satisfactory.

Other complications of treatment with levodopa can include **dyskinesia**, which may respond to dosage adjustment or partial replacement of levodopa with a dopamine agonist. Amantadine may also be considered, although evidence is lacking. Some patients with Parkinson's disease may experience **severe pain** and **dystonia**; measures to increase 'on' periods can help reduce or eliminate pain in most patients.

Patients with Parkinson's disease can suffer from a range of **psychiatric effects**, such as depression, dementia, sleep disturbances, and psychosis, due to the adverse effects of drug therapy and to disease progression. It has been recommended that if patients develop psychotic reactions, an attempt to adjust their antiparkinsonian drugs should be tried before resorting to the use of antipsychotics. Although classical antipsychotics are usually contra-indicated because they can exacerbate parkinsonism, the atypical antipsychotics clozapine and quetiapine may be used in treatment-resistant psychosis—see Disturbed Behaviour, p.954. The cholinesterase inhibitor rivastigmine is licensed in some countries for the symptomatic treatment of mild to moderately severe dementia in Parkinson's disease. **Excessive daytime sleepiness** and **sudden onset of sleep** have been reported with dopamine agonists and patients should be warned of the possible risks (see Effects on Mental Function, under Adverse Effects of Levodopa, p.805). **Fibrotic reactions** resulting in cardiovascular and pulmonary adverse effects have been reported with ergot derivatives and patients should be monitored (see Fibrosis, under Adverse Effects of Bromocriptine, p.799). **Nausea and vomiting** induced by dopaminergics may be minimised by introducing the drug gradually and giving the dose with food, but if this is ineffective or apomorphine is being used these effects can be controlled by the antiemetic domperidone. Domperidone does not readily cross the blood-brain barrier and therefore acts mainly as a peripheral dopamine antagonist. Tolerance to the nausea usually develops after a few weeks and domperidone may then be withdrawn.

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Amantadine *(BAN, pINN)*

Amantadiini; Amantadin; Amantadina; Amantadinum. Tricyclo[3.3.1.1^{3,7}]dec-1-ylamine.

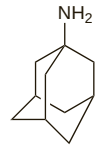
Амантадин

$C_{10}H_{17}N$ = 151.2.

CAS — 768-94-5.

ATC — N04BB01.

ATC Vet — QN04BB01.



Amantadine Hydrochloride *(BANM, USAN, pINNM)*

1-Adamantanamine Hydrochloride; Amantadiinihydrokloridi; Amantadine, chlorhydrate d'; Amantadin-hidroklorid; Amantadin-hydrochlorid; Amantadinhydroklorid; Amantadini hydrochloridum; Amantadino hidrochloridas; EXP-105-1; Hidrocloruro de amantadina; NSC-83653. Tricyclo[3.3.1.1^{3,7}]dec-1-ylamine hydrochloride.

Амантадина Гидрохлорид

$C_{10}H_{17}N,HCl$ = 187.7.

CAS — 665-66-7.

ATC — N04BB01.

ATC Vet — QN04BB01.