Dopamine agonists act directly on the postsynaptic receptors. They are more expensive than levodopa, difficult to titrate to maximal effect and have lower tolerability and efficacy. However, studies using pramipexole, ropinirole and pergolide have shown a 50% reduction in motor complications compared to levodopa. Their place in therapy is two fold, either as initial monotherapy (so called levodopa sparing) or as an adjunct to levodopa in the later stages of disease when motor control has deteriorated. The most common side effects are nausea and vomiting that can be treated with domperidone, postural hypotension, hallucinations, confusion and exacerbation of dyskinesias. The dopamine agonists more commonly cause psychiatric side effects than levodopa particularly in the elderly. The ergot derivatives (bromocriptine, cabergoline and pergolide) may cause pleuropulmonary fibrosis in ~2-6% on long-term treatment. Annual monitoring with chest x-rays and ESR have been recommended for patients taking an ergot derivative.
**Which dopamine agonist?**

There are more similarities than differences between the dopamine agonists\(^8\). All the newer agents (cabergoline, pergolide, ropinirole, pramipexole) have been shown to be slightly better than bromocriptine. However, there have been very few comparative studies of dopamine agonists so it is not possible to be definitive as to which drug should be recommended (see table 3). Each has a similar incidence of dopaminergic side effects, although there is considerable inter-patient variability in terms of both efficacy and tolerability. A meta-analysis comparing the risk of adverse events with ropinirole and pramipexole found that somnolence and hypotension was more common with ropinirole than pramipexole, but hallucinations were more common with pramipexole.\(^20\) Cabergoline has the fastest titration schedule (maintenance dose can be reached in 2 weeks) and because of its long half-life can be given once a day, which may be advantageous for some patients. Pramipexole can be titrated to therapeutic dose in 3 weeks and some studies have shown that it may improve symptoms of depression\(^21\), although this was not a primary end point. Ropinirole and pergolide have the slowest titration schedules (8 and 4-6 weeks respectively), however, starter packs are now available for these two drugs which simplify both prescribing and administration.

**Initiating a dopamine agonist**

It is recommended that a specialist Parkinson's Disease team (including PD specialist nurses) start dopamine agonists. In order to minimise side effects, dopamine agonists should be started with low doses and titrated up slowly.

**Initial therapy with levodopa or dopamine agonist or other agent?**

The choice of first line agent for treatment of PD is controversial. A minority of younger patients with tremor predominance can be initially treated with anticholinergics. For all other patients and those with contra-indications to anticholinergics, the decision is which dopaminomimetic. Biological age, co-morbidity, cognitive impairment and disease severity are all factors that should be considered. Dopamine agonists are generally considered the first line agents for biologically young fit patients without co-morbidity and a life expectancy > 15 years in order to reduce the risk of motor fluctuations in the long term. Levodopa may be considered the first line option for biologically older or frail patients with a history of cardiac or psychiatric disease.

**COMT inhibitors**

Entacapone is a peripheral catechol-o-methyl transferase (COMT) inhibitor. COMT is an enzyme involved in the metabolism of levodopa and dopamine. When levodopa is given with a DDI, some levodopa is still lost as a result of breakdown by COMT. This reduces the amount of levodopa available for conversion to dopamine in the brain. There is no evidence that entacapone has an effect on endogenous dopamine, it functions only in the presence of externally administered levodopa and should be administered with each dose of levodopa. It can be used to extend the benefits of levodopa. The peak Cmax of levodopa is unaltered, but duration of action is increased leading to a reduction in motor complications and a reduction in levodopa dose of 10-30% should be anticipated.\(^10\) In a typical patient the addition of entacapone can increase ‘on’ time by an average of 90 minutes.

**Selegilene**

This is a selective, irreversible MAO type B inhibitor that slows the breakdown of dopamine in the striatum. It provides only modest symptomatic benefit. It may have a role similar to entacapone in extending the duration of action of levodopa therapy. It should be administered in
the morning to prevent insomnia caused by its amphetamine metabolites. The lyophilisate formulation of selegiline is absorbed buccally and is not only useful for patients with swallowing difficulties, but metabolite generation is reduced. Selegiline 10mg tablets are therapeutically equivalent to 1.25mg orally absorbed lyophilisate tablets. The safety of selegiline was called into question by a single trial that showed increased mortality in combination with levodopa

Amantadine

Amantadine is an antiviral agent with a modest antiparkinsonian effect. It is thought to have an action in the glutaminergic system as an N-methyl-D-aspartate (NMDA) antagonist and it now reserved for the treatment of dyskinesias in advance disease. Caution is necessary in older patients and those with renal impairment. Side effects include confusion, hallucinations, peripheral oedema and livedo reticularis. The usual starting dose is 100mg daily increased to twice daily if tolerated. Some patients may require higher doses and the maximum licensed dose is 200mg twice daily.

Anticholinergics

The use of anticolinergics e.g. benzhexol predates use of levodopa. However due to troublesome side effects (cognitive impairment, urinary retention, glaucoma, hallucinations and frank confusional states) their use is now limited to selective younger patients with predominant tremor. Use in patients over 60 years is not recommended.

Prepared by:
Ralph Gregory, Consultant Neurologist          Ali Harris, Neurosciences Pharmacist

References
<table>
<thead>
<tr>
<th>Drug</th>
<th>Ergot</th>
<th>Receptor affinity</th>
<th>Half life</th>
<th>Elimination</th>
<th>Licensed indications</th>
<th>Initial dose</th>
<th>Titration schedule</th>
<th>Min Time to maintenance dose</th>
<th>Maintenance dose range</th>
<th>Typical dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>Yes</td>
<td>D1, D2, Alpha, 5HT3</td>
<td>3-4 hours</td>
<td>Inactive metabolites.</td>
<td>For Parkinsonism</td>
<td>1.25mg at night for 1 week then 2.5mg at night for 1 week</td>
<td>Increase TDD by 2.5mg every week</td>
<td>4 weeks</td>
<td>10 to 40mg daily in 3 divided doses</td>
<td>£68.60 for 30mg daily</td>
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<tr>
<td>Pergolide</td>
<td>Yes</td>
<td>D1 and D2</td>
<td>24 hour</td>
<td>Active metabolites</td>
<td>Adjunct or mono-therapy</td>
<td>50microg at night for 1-2 days</td>
<td>Increase every 3 days. Regimen is dependant on whether L-dopa is co-prescribed</td>
<td>4 weeks monotherapy 6 weeks adjunctive therapy</td>
<td>1.5 to 5mg in 3 divided doses</td>
<td>£145.23 for 3mg daily</td>
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<tr>
<td>Cabergoline</td>
<td>Yes</td>
<td>D2</td>
<td>65 hour</td>
<td>Weakly active metabolites</td>
<td>Adjunct to L-dopa only</td>
<td>1mg daily</td>
<td>Increase TDD by 0.5-1mg every 1-2 weeks</td>
<td>2 weeks</td>
<td>2 to 6 mg daily</td>
<td>£155.95 for 4mg daily</td>
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<tr>
<td>Ropinirole</td>
<td>No</td>
<td>pure D2</td>
<td>6 hour</td>
<td>Weakly active metabolites</td>
<td>Adjunct or mono-therapy</td>
<td>250microg tds for 1 week</td>
<td>Increase TDD by 750mcg every week</td>
<td>8 weeks</td>
<td>6 to 24mg in 3 divided doses</td>
<td>£289.52 for 20mg daily</td>
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<td>Pramipexole</td>
<td>No</td>
<td>D3 and D2</td>
<td>8-12 hour</td>
<td>Mostly unchanged in the urine</td>
<td>Adjunct or mono-therapy</td>
<td>125microg salt tds for 5-7 days</td>
<td>Double the dose every 5-7 days</td>
<td>3 weeks</td>
<td>1.5 to 4.5mg in 3 divided doses</td>
<td>£314.22 for 4.5mg (as salt) daily</td>
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<tr>
<td>Apomorphine</td>
<td>No</td>
<td>D1, D2 and D3</td>
<td>1 hour</td>
<td>Inactive metabolites</td>
<td>Refractory fluctuations</td>
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<td></td>
<td></td>
<td></td>
<td>£501.07 + diluent/syringe etc, for 50mg per day/sc infusion</td>
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