A short history of dopamine agonists

The discovery of dopamine deficiency as a cause of the disability of Parkinson’s disease has led to an era of successful dopaminergic therapy. Professor Jeremy Playfer provides an overview of the evolution of dopamine agonists and their use, starting from the 1960s through to what innovative new therapy options are available today and which may best suit the older patient in the early and late stages of the disease.

Most classes of drug have a life cycle, as described by Professor DR Laurence in his textbook in the 1960s. In a simple sketch he showed that initially the use of a new compound was restricted to clinical trials; once launched, the use of the drug increased rapidly until it reached a peak when its limitations and side effects became more evident and competition would possibly come into play. The decline was usually in two phases; first, a fairly rapid rise to the point where the drug reached a ‘steady state’, then a slow drift downward as it found its niche within the therapeutic area. This pattern is well illustrated in the drugs used for Parkinson’s disease (PD). Dopaminergic therapy in the form of levodopa first came into use in the mid-1960s. However, its take-off was slow due to the cost the drug and the fact it induced nausea and vomiting, limiting its value.

In the early 1970s, decarboxylase inhibitors made use of these drugs easier and the price came down. For the next 20 years Sinemet® and Madopar® dominated the therapy of PD. In longer-term use it became apparent that a high percentage of patients on levodopa alone developed motor complications, particularly dyskinesias and motor fluctuations. Practitioners in the late 1970s and 1980s tried to use adjunct therapy to overcome the limitations of levodopa, both in the length of action and propensity to cause abnormal involuntary movements. For a time, selegiline was a very successful and widely used drug in PD, and the first generation of dopamine agonists were used in addition to levodopa. The first to make a major impact was bromocriptine. Following the innovative work by Andrew Lees and Gerald Stern, bromocriptine was used as a single agent in the management of PD.

Andrew Lees’ original trial showed 70 per cent of patients could not tolerate the drug alone for more than 12 months. Psychiatric complications were particularly common, especially hallucinations and vivid dreams. Teychenne initiated a regimen of low dose bromocriptine to overcome these side effects; however, in spite of...
initial optimistic reports of the effectiveness of low-dose dopamine agonists, subsequent trials showed this regimen ineffective. In spite of this setback, the theoretical arguments for the use of dopamine agonists were increasingly compelling. They act directly on dopamine receptors and therefore are not dependent on the degenerating dopaminergic cells. With a greater understanding of the different families of dopamine receptors, came the possibility of targeting D2 class receptors.

An even greater stimulus to the use of these drugs was the theoretical possibility that by reducing dopamine turnover and oxidative stress, they might be neuroprotective and modify the course of the disease. Newer ergot-derived dopamine agonists emerged in the form of lisuride, cabergoline and pergolide. Pergolide was — and still is — an extremely potent and effective dopamine agonist and soon became the market leader. Subsequently non-ergot derivatives — apomorphine (only used parenterally), pramipexole and ropinirole — reached the clinical stage. The use of dopamine agonist required high levels of clinical skill. Intolerance was quite common, particularly in relation to the ergot-derived drugs, which often cause gastrointestinal side effects — nausea, vomiting, anorexia — and autonomic features, such as postural hypotension, as well as mental side effects in the form of hallucinations and somnolence. Slow titration, facilitated by starter packs for pergolide and ropinirole, made the drugs easier to use.

There is a great tendency to under-dose on dopamine agonists, resulting in the worsening of motor symptoms initially. How this worked was elegantly demonstrated by Malcolm Steiger, who demonstrated that at low doses dopamine agonists inhibited the re-uptake of dopamine by neurones and also reduced the effect of endogenous dopamine. The occurrence of fibrotic and serosal events associated with ergot-derived dopamine agonists came to the attention of the Committee of Safety of Medicine and led to a dramatic reduction of the use of ergot-derived dopamine agonists. Although there is still some controversy regarding frequency and severity of these effects, it is clear they can on occasion cause cardiac valvulopathy and retroperitoneal fibrosis as well as pulmonary fibrosis.

As these disadvantages emerged, evidence for the non-ergot derived dopamine agonists ropinirole and pramipexole strengthened. In 2000, Rascol et al. published results of a five-year randomised levodopa controlled trial of ropinirole and demonstrated initial monotherapy use of ropinirole reduced incidence of motor side effects by half. This was probably one of the most important papers in the history of the therapy of PD and since its publication non-ergot dopamine agonists became regularly used in de novo patients as first-line monotherapy. A follow-up trial in 2005 demonstrated that initiation on a dopamine agonist can deliver long-term benefits associated with lower incidence and delayed onset of dyskinesias 10 years after the commencement of therapy.

There is a strong argument for using dopamine agonists as first-line therapy in younger patients, where the risk of motor fluctuations is greatest and their greater expectation of life inevitably means they will develop motor complications on levodopa. In the elderly patient, the argument is slightly different. It is shown that they are less likely to get motor fluctuations and more likely to get psychiatric complications, particularly hallucinations. In the monotherapy trials, even in a young population screened for cognitive impairment there was still a much higher rate of psychiatric side effects on dopamine agonists. For awhile, there was a consensus that dopamine agonist should be used first in younger patients and levodopa in older ones. With greater clinical confidence in dopamine agonists, opinion has shifted and there is little hesitation in starting the robust elderly on a dopamine agonist if it is judged their risk of motor complications is significant.

Their use is increasing because the importance of achieving continuous dopaminergic stimulation, accepted as being a guiding principle of drug therapy. The limitations of levodopa are largely explained by its short half-life. Although this may be ameliorated by adjunct therapy with COMT (catechol-o-methyltransferase) inhibitors or monoamine oxidase inhibitors (MAOIs), the two principle dopamine agonists, ropinirole and pramipexole, have longer half-lives and can achieve continuous dopaminergic stimulation on monotherapy. This is almost certainly the reason why motor fluctuations and dyskinesias are less prevalent. More importantly, the full benefit of sparing motor complications is improved if patients have not been exposed to levodopa prior to the introduction of a dopamine agonist. Even patients in the late stages of the disease can have motor complications improved by achieving continuous dopaminergic stimulation. The use of
apomorphine subcutaneously — either as a pen jet rescue or as a continuous infusion — have proved this point beyond doubt. Methods of continuously infusing levodopa are expensive and require advanced systems of care. We are likely to be dependent for some time on using standard non-ergot dopamine agonists.

Recent trial data, presented at the European Federation of Neurological Societies (EFNS) relating to a new once-a-day formulation of ropinirole show that it is at least as effective as currently available ropinirole, which is administered three-times daily, in terms of providing effective symptom control for patients with early PD	extsuperscript{4}. The improved pharmacokinetic profile of ropinirole prolonged release leads to a more continuous stimulation of the dopamine receptors and permits once-daily dosing.

Another recent addition to the dopamine agonist class was introduced early this year. Rotigotine, a dopamine receptor-agonist formulated as a transdermal delivery system through skin patch, is designed for once-a-day application. There are benefits for certain patients through the convenience of once-daily dosing as well as a simple titration scheme	extsuperscript{5}. Rotigotine has also been shown to be superior to placebo in two randomised controlled trials. However, one study of this method of delivery was less effective than oral therapy with ropinirole — a study cited by the Scottish Medicine Consortium recently as its justification for non-approval and one that raises questions on efficacy	extsuperscript{6}.

### Key points

- Dopamine agonists are well established in the treatment of PD and have been demonstrated to reduce longer-term motor complications when given as initial therapy.
- Caution is needed using dopamine agonists in older frail patients due to increased risk of psychiatric side effects.
- Evidence for neuro-protection with dopamine agonists remains controversial and inconclusive.
- Newer methods of delivery of dopamine agonists such as transdermal patches offer a newer way of achieving continuous dopaminergic stimulation.

### References

8. Ropinirole Summary of Product Characteristics, September 2002
12. Rascol O, Brooks DR, Korczyn AD, et al. A five year study of the incidence of dyskinesias in patients with early Parkinson’s disease who were treated with ropinirole or levodopa. NEJM 2000;342:1484-1491

### Conclusion

Over the last 30 years we have seen dopamine agonists come and go. The use of ergot-derived dopamine agonists is declining rapidly. Initiation of therapy on these drugs is now difficult to justify. The synthetic dopamine agonists ropinirole and pramipexole are now firmly embedded in the standard method of managing PD. The present state of play was well stated in the recent National Institute for Health and Clinical Excellence (NICE) guidelines	extsuperscript{4}: ‘There is no single drug choice for the initial pharmacotherapy of early PD’ and ‘it is not possible to identify a universal first choice drug therapy to people with PD’. Dopamine agonists have class A evidence for use of symptomatic treatment in patients with early PD.
Caution has to be taken using ergot-derived dopamine agonists, as patients will require renal function tests, ESR (erythrocyte sedimentation rate), and chest x-rays performed before treatment and annually thereafter. While it is recognised that in later PD levodopa therapy will almost always be required, class A evidence is recognised for dopamine agonists to reduce motor complications in these patients\(^1\). One exciting development is that just as dopamine agonists have reached their ‘steady state’ in treating PD, a new clear and compelling indication has arisen for restless legs syndrome. Recently both ropinirole and pramipexole have been approved in the UK for treatment of this condition.

In looking at older patients, clinicians should now not be frightened of using dopamine agonists. In early PD there will still be a debate as to whether levodopa or a dopamine agonist is the most appropriate for an individual patient. Age is certainly still a factor in this decision — more so frailty, which favours levodopa. The choices for adjunct therapy of levodopa are more complicated but there is firm evidence the longer acting dopamine agonists are very effective as ameliorating motor complications in late disease\(^1\). Again, the choice against a MAOI or a COMT inhibitor can be difficult and is probably largely based on the robustness of the patient and their other co-morbidities. Particularly important in the selection of a dopamine agonist is the absence of significant psychiatric symptoms, especially hallucinations or sleep disorders. With their place firmly entrenched in the management of PD, future developments in the use of dopamine agonists are likely to strengthen their position. The recent introduction of a dopamine agonist skin patch for adjunctive use is not only an interesting development, but awaits stronger evidence. There is eager anticipation of a controlled release preparation of dopamine agonists with the development of this product at an advanced state for ropinirole.

These and other developments mean that ropinirole and pramipexole will remain quite central to the management of PD in the older patient.

**Conflict of interest:** Professor Playfer has provided professional advice and received payment for lectures from most of the pharmaceutical companies producing drugs for Parkinson’s disease.