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Teaching Monograph: *A Grand Round Series*

An ongoing clinical series exploring emerging areas for psychiatrists and neurologists

Current Uses of Dopamine Agonists

Moderator

Andrew Lees, MD, FRCP

Discussants

Treatment of Parkinson's Disease Using Dopamine Agonists

Peter Jenner, MD, Bpharm, PhD, DSc, FRPharmS

Treatment of Restless Legs Syndrome Using Dopamine Agonists

Claudia Trenkwalder, MD

An MBL Project

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ABSTRACT

The advent of dopamine agonists may provide a way to avoid treating patients with levadopa, and thereby avoiding dyskinesias and motor fluctuations altogether.

Dopamine agonists have proven an effective treatment in Parkinson's disease (PD) and restless legs syndrome (RLS); today more and more doctors use agonists and lower doses of levodopa and see the degree of dyskinesia decrease in patients. Since the appearance of a newer generation of agonists on the market—Requip, Mirapex, Cabergoline—debate arises as to whether any real difference exists between new and old. Permax, one of the older agonists, is by far the strongest, and when studying its receptor activity (D_2), it is difficult to know whether its performance is surpassed by that of another agent.

In studying PD, a stark deviation is apparent in clinical efficacy and in the production of dyskinesia between treatment with dopamine agonists and L-dopa. Dopamine agonists cause the least dyskinesia, have fewer side effects, and are therapeutically effective in the long-term. Also, beginning treatment with levodopa may mean the onset of dyskinesia regardless of whether a switch is made afterward to a dopamine agonist. With RLS, patients who were given Permax reported a longer symptom-free period than they did when taking levodopa. It would seem that efficacy in treating PD may be explained by a correlation between dopamine and opiate systems, and/or by the presence of dopamine receptors in either or both the brain stem and spinal cord.

DISCLAIMER

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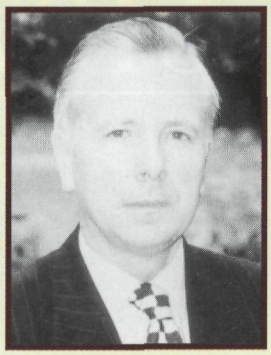

Andrew Lees is a staff neurologist at the University College London Hospitals. He is director of the Parkinson's Disease Society Brain Research Centre and Francis and Renee Hock Director of Research at the Reta Lila Weston Institute of Neurological Studies. He is co-editor-in-chief of the *Movement Disorders Journal* and chairman of the Scientific Panel on Parkinson's disease of the European Federation of Neurological Societies. He is also the chairman of the Parkinson's Disease Research Group of the United Kingdom.

Peter Jenner is head of the Division of Pharmacology and Therapeutics in the Guy's, King's & St. Thomas' School of Biomedical Sciences at King's College in London. He is a director of the Neurodegenerative Disease Research Centre and the National Parkinson Foundation Centre of Excellence. He has contributed significantly to the concept of oxidative stress as a cause of the progression of nigral cell death in Parkinson's disease. In addition, he has been responsible for developing novel compounds for the treatment of Parkinson's disease and the avoidance of dyskinesia through the use of experimental models of the illness. Professor Jenner is a member of the Council of the Parkinson's Disease Society of the United Kingdom and he regularly talks to lay audiences at branches of the Society.

Claudia Trenkwalder is assistant professor of neurology at the Ludwig Maximilian University of Munich, where she was trained in clinical neurology, neurophysiology, movement disorders, Parkinson's disease, Wilson's disease, Huntington's chorea, and restless legs syndrome. Since 1993 she has been head of the Neurological Ward and Intermediate Care Unit at the Max Planck Institute of Psychiatry, as well as head of a research group that studies movement disorders and sleep. Dr. Trenkwalder has also participated in research projects in cooperation with national and international movement disorder groups.

Style Note: This teaching monograph is intended to replicate a scientific symposia, where experts in a particular field advise their colleagues about new developments. While CNS Spectrums *uses generic names throughout, this work references trade names to ease the give and take between discussants, and to help make the advice herein more palatable to either psychiatrists or neurologists, both of whom share equally the advances described herein. —The Editors*

DISCUSSION

Andrew Lees, MD, FRCP

Introduction

I discussed the use of dopamine agonists in the treatment of Parkinson's disease (PD) with Dr. Peter Jenner and restless legs syndrome with Dr. Claudia Trenkwalder. Although I have not been directly involved in the clinical trials with restless legs syndrome, I use dopamine agonists in routine clinical practice with PD and find them to be extremely effective. Many patients have tried medications such as benzodiazepines, Tegretol, analgesics, and antidepressants—almost everything in the pharmacopeia—without marked success; patients then take dopamine agonists and, for the first time in many years enjoy a great improvement.

In patients with PD under the age of fifty I usually start with an agonist. Once a patient has developed levodopa-induced dyskinesias, even if levodopa (L-dopa) is completely withdrawn and an agonist prescribed, they still get dyskinesias. However, for the average patient aged sixty, I start with small doses of L-dopa. When the patient begins to escape from control, which is usually 1 to 3 years into L-dopa treatment, I add an agonist rather than increase dosage. It's debatable whether everybody should be started on an agonist or started with L-dopa and have an agonist added later. We're introducing agonists earlier than we were 10 years ago.

Treatment of Established Dyskinesia

The first thing to do is control an established dyskinesia. An attempt should be made, assuming the patient is on L-dopa, to reduce the dose. Then, add an agonist and try to reduce the L-dopa further. If that doesn't work, Symmetrel is something very easy to try now. I think it is getting used quite a lot fairly early on, even though more trials are needed. If neither methods work, our group has been particularly interested in continuous dopaminergic stimulation with apomorphine subcutaneous infusions, administered by an ambulatory mini-pump. Constant subcutaneous apomorphine monotherapy decreases the intensity of dyskinesia. In fact, one seems to be able to reset the dyskinesia threshold although it may take several weeks or months to do so. L-dopa cannot be drastically reduced immediately, so in a patient on L-dopa who has bad dyskinesia, reduce dosage gradually by 50 mg a week.

One interesting question is why, with the deep cerebral stimulation, can you not get rid of L-dopa completely? Could it be due to pleasure and reward systems in the brain? Stimulation of the mesocorticolimbic dopamine systems of the brain by chronic L-dopa may lead to increased motivation and "mental highs" during which the patient becomes dependent. I believe this is much more prevalent than we have recognized in clinical practice.

The Future of Dopamine Agonists

Dopamine is very potent in gating a whole range of processes. If it is indeed involved in gating mechanisms, it will control levels of many forms of behavior as well as movement addictive tendency—this might be the role of dopamine in the brain. But it's quite a philosophical issue. The more we look at dopamine and dopaminergic mechanisms, the more relevance we find in biological psychiatry.

The problem with the dopamine agonists is they do have early adverse events. The general view is that although individual patients may get comparable effects to L-dopa in the early stages of the disease, generally they are not as strong as optimum doses of L-dopa.

We clearly need more potent dopamine agonists with fewer side effects, and it should be possible to develop these. The hope for dopamine agonists is there may be a way to avoid treating patients with L-dopa and thereby avoiding dyskinesias and motor fluctuations altogether.

Although there are six of these agonists now available, I would like to encourage the industry to keep working in this field so that we have even more powerful agents with long durations of action. CNS

DISCUSSION

Peter Jenner, MD, Bpharm (Hons), PhD, DSc, FRPharmS

Treatment of Parkinson's Disease Using Dopamine Agonists

In treating Parkinson's disease (PD) the big questions are: Why is there a difference in clinical efficacy and the production of dyskinesia between levadopa (L-dopa) and dopamine agonists? What are the roles of the various dopamine receptors present in the brain? And, if we can selectively stimulate those dopamine-receptor subpopulations, can we produce therapeutic benefit with dopamine agonists while eliminating their side effects and also avoiding the side effects that are produced by L-dopa in the current treatment of PD?

In my experimental studies, in which drug-naive MPTP-treated (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) primates are used, administration of L-dopa quickly, over a period of 2 to 3 weeks, induces marked dyskinesia. In contrast, in this experimental model of PD, treatment with a dopamine-agonist over the same period produces little or no dyskinesia. One would expect that if animals or patients are treated with a D_1-D_2 dopamine agonist, the effects of L-dopa itself would be mimicked. But clearly, from both the effects on Parkinson's and in the induction of dyskinesia, this isn't true.

It is feasible that since L-dopa is the best drug for treating the symptoms and for inducing dyskinesia, that perhaps it does something different than dopamine agonists. I don't think that pure dopaminergic-receptor stimulation explains subsequent dyskinesia. I believe there are other biochemical or neurochemical components to the onset of dyskinesia.

Another important point when considering using dopamine agonists is you lose the window of opportunity for their use once patients have been exposed to L-dopa for short periods of time. If I prime my monkeys with L-dopa, they all get dyskinesias when I acutely challenge them with dopamine agonists. This happens clinically as well.

If we want to avoid dyskinesias, we have to use other therapeutic strategies initially in treating PD, such as using dopamine agonists as monotherapy, turning our attention to L-dopa only when the patient requires it.

The New Generation of Dopamine Agonists

Certainly today more doctors are using agonists and lower doses of L-dopa than previously. When I visit patient groups at lay meetings, the degree of dyskinesia I see is much less than it was 20 years ago. I no longer face a sea of writhing limbs,only the occasional affected patient, usually with young onset disease.

It seems that dopamine agonists are very useful initially as monotherapy for avoiding dyskinesia, and the use of dopamine agonists by subcutaneous infusion is helpful for resetting the dyskinesia threshold.

Some dopamine agonists, like Parlodel, Permax, and apomorphine, have been around for a long time. Now we're seeing a new generation of dopamine agonists, like Requip, Mirapex, and Cabergoline. Some of these are said to be selective for the D_3 receptor, but I question whether there is any real difference between the new and the older generation of dopamine agonists.

Permax is undoubtedly the most potent of the agonists and has the longest duration of effect. But when one studies its receptor pharmacology, it's difficult to see a difference. On the D_2-like family of receptors, it is clear that Parlodel, Permax, Requip, and Mirapex all interact functionally with both D_2 and D_3 receptors. I don't see any real difference between these drugs, although some patients do better on one dopamine agonist compared to another.

Curiously, Permax and apomorphine are both functionally effective in stimulating D_1 receptor populations and may have added advantages in terms of the antiparkinsonian activity of these compounds and their side-effect profile. The two also might have other benefits in patient populations, such as an ability to leave cognitive function either unimpaired, or to improve cognitive and bladder function.

Potential Uses of Dopamine Agonists

Dopamine agonists may have many indications we don't yet know about. The agonists are being used to treat restless legs syndrome and alcoholism. They may be useful in preventing drug addiction. There may be a host of other indications for these drugs that have not been exploited.

When we understand the nature of the various subtypes of dopamine receptors and their localization in the brain, and when we have the ability to use selective agonists and antagonists on these receptors, we will discover the function of the new dopamine receptor families—the D_1, D_2, D_3, D4 and D5. At that juncture, I believe we're going find that dopaminergic drugs are useful in many disorders. CNS

DISCUSSION

Trenkwalder, MD

Treating Restless Legs Syndrome with Dopamine Agonists

I began to use dopamine agonists in restless legs syndrome (RLS) after I saw that patients who were on an increased dosage of levodopa (L-dopa), up to 800 or 1,000 mg, were still not symptom-free and in fact felt symptoms during the day they didn't have before taking L-dopa. This side effect, called augmentation, is the main reason to switch to dopamine agonists.

Treatment Studies with Permax in RLS

In a study we conducted, patients were switched from L-dopa to Permax and given a single bedtime dose of Permax 2 hours before falling asleep. This resulted in a longer symptom-free period during both day and nighttime for the patients. We started with a low dosage—.05 mg of Permax—and increased the dosage by .05 mg per day. We also gave domperidon (Motilium), to avoid gastrointestinal side effects. If Motilium is not available, as is the case in the United States, Permax is still useful, but one must increase the dosage more slowly and give half tablets of .05 mg.

In the next controlled study we saw Permax was an effective treatment not only for the subjective restless legs symptoms but for reducing the periodic limb movements and the periodic limb movement arousal, which are very high in RLS during sleep. The benefits lasted for the entire night (8 hours). Most of the patients took one dosage of Permax before bedtime and didn't need a second dosage during the night. In most patients the effect lasted the entire following day as well.

Individual Therapy Regimen for RLS Patients

We try to give each patient an individual treatment regimen. Young patients who don't need treatment all day are best treated with L-dopa. The difference is one can give L-dopa as a single dose when it is necessary, which you cannot do with dopamine agonists. Patients with moderate or severe RLS who need all-night treatment and who also report daytime symptoms should be treated with Permax. It is also helpful to give one or two dosages of L-dopa just before starting Permax treatment in order to determine whether the patient responds to dopaminergic treatment. There is a very quick response in which the level of efficacy is apparent within the first or second night. Then treatment can be optimized and Permax increased if necessary. In most cases, one should start with the .05 mg of Permax and gradually increase the dosage to 0.25–0.5 mg until the patient is symptom-free.

Why Are Dopamine Agonists Effective?

In terms of why dopamine agonists are effective in treating RLS, all we know about the pathophysiology from treatment studies is that the dopamine system and the opiate system together play a major role in this disorder. Efficacy could also be related to dopamine receptors in the brainstem or the spinal cord, or both. We don't have a good argument to say that dopamine agonists are working by this striatal dopamine system, as in PD, but perhaps it's more the reduction of spinal disinhibition—which we know occurs in RLS—measured by neurophysiological studies. However, there is no good theory to say why dopamine agonists or L-dopa really works in RLS.

We now know that we can treat patients for 1 or 2 years with Permax, but we need long-term studies to say that Permax is a long-term treatment, because RLS is a chronic disorder and needs continuous treatment. In PD, the studies measuring neuroprotection—the PET studies—will hopefully give us more data to see if dopamine agonists are neuroprotective drugs. This will be a further argument to start early treatment with dopamine agonists in the future. CNS

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CNS 99.1.01

Theoretical Advantages of Dopaminergic Agonists

- Improved specificity
- Longer duration of action
- Less gastrointestinal competition for absorption
- Avoids need for central dopa decarboxylase
- Active and potentially toxic metabolites not produced

Lees A. *CNS Spectrums.* Vol 4, No 1. 1999.

CNS 99.1.02

Are Dopamine Agonists Neuroprotective?

- Felten et al have shown that pergolide fed to rats over a 18-month period slows the age-related loss of nigro-sriatal dopamine neurons.
- Clow et al have shown that pergolide increases the striatal level of superoxide dismutase, a naturally occurring free-radical scavenger.

Lees A. *CNS Spectrums.* Vol 4, No 1. 1999.

CNS 99.1.03

Rationale for the Later Use of Dopamine Agonists

- Levodopa is the most effective symptomatic treatment available; therefore, it is unethical to withhold it
- Agonists are not as good as levodopa to provide symptomatic relief
- Evidence for the neurotoxicity of levodopa is not conclusive
- No direct evidence for the oxidative stress hypothesis

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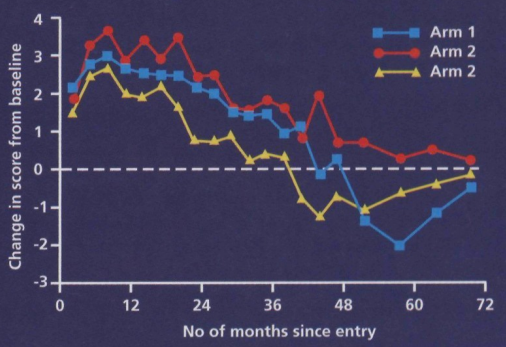
Average Change in Webster Score by Treatment Group in Patients With Parkinson's Disease



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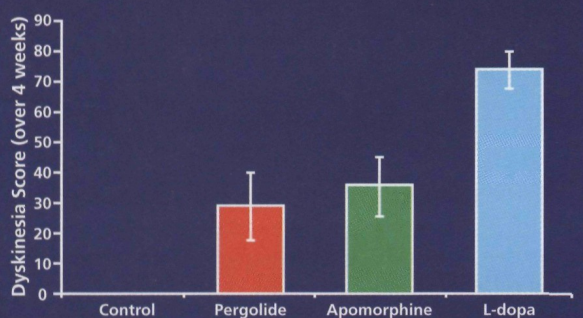
Cumulative Dyskinesia Score



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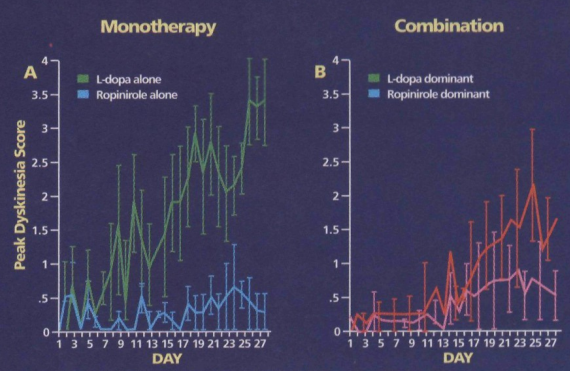
L-dopa and Ropinirole in Monotherapy and Combination



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Dopamine Receptor Stimulation and Dyskinesia

- L-dopa induces profound dyskinesia
- Short-acting dopamine agonists producing a pulsatile effect induce marked dyskinesia
- Long-acting dopamine agonists which produce continuous receptor stimulation do not induce marked dyskinesia
- Both D_1 and D_2 agonists have similar effects
- Once dyskinesia is established, both D_1 and D_2 agonists induce dyskinesia by the intensity with D_1 agonists is less marked

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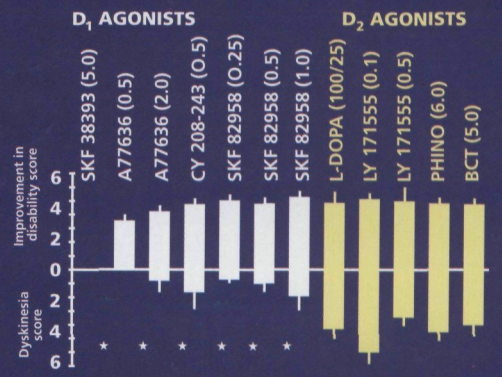

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Restless Legs Syndrome: Diagnostic Criteria

(International Restless Legs Syndrome Study Group, 1995)

Minimal criteria:

- Desire to move the limbs usually associated with paresthesias/dysesthesias
- Motor restlessness
- Symptoms are worse or exclusively present at rest (ie, lying, sitting) with at least partial and temporary relief by activity
- Symptoms are worse in the evening/night

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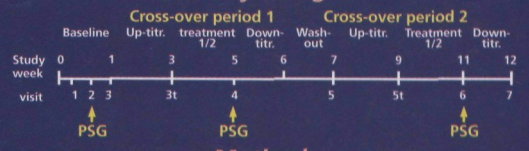
Treatment of RLS with Pergolide

Study Design



Methods

Polysomnography:
- At baseline and at the end of both treatment periods; parameters were quantified by standard criteria

(Rechtschaffen & Kales 1968, Coleman 1982, ASDA 1993)

Subjective ratings:
- Sleep inventory SF-A before and after PSG
- Severity of RL symptoms at each visit
- Quality of life (during previous week of each period)
- Sleep diary

Ratings of the investigators:
- Clinical Global Impression Scales (CGI)

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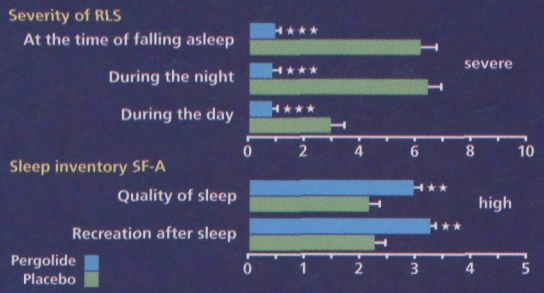
Severity of RLS: Pergolide vs Placebo



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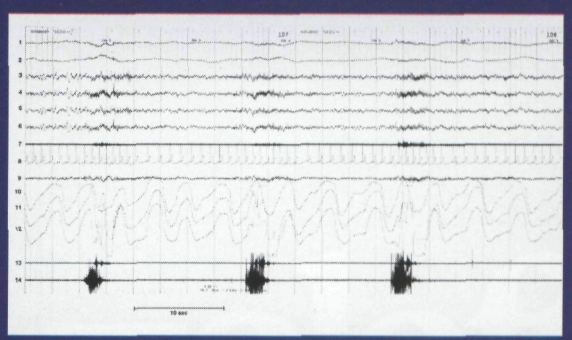
PLM - Sleep EEG



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