

## 'BAD GUYS' AMONG THE ANTIPARKINSONIAN DRUGS

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### SUMMARY

The first effective drugs for Parkinson's disease (PD) were anticholinergics, introduced at the end of 19.th century by Charcot. Since the introduction of levodopa in the sixties of the previous century, many new drugs have emerged for the treatment of Parkinson's disease: dopamine agonists (ergot as well as non-ergot, bromocriptine, pergolide, mirapexine, ropinirole), MAO B inhibitors (selegiline, rasagiline), amantadine, COMT inhibitors (entacapone, tolcapone).

In all stages of the disease, levodopa remains the most effective drug for improving motor symptoms in PD. However, long term treatment with levodopa is accompanied by the development of motor fluctuations, dyskinesia, cognitive and neuropsychiatric adverse effects and increasingly diverse spectrum of drugs is needed to alleviate motor and nonmotor symptoms.

Some of these drugs have caused considerable concern and controversies and were regarded at certain points as the 'bad guys' of Parkinson's disease pharmacological armamentarium. In the article, a short review of 'bad guys' including anticholinergics, selegiline, tolcapone and dopamine agonists, is given.

**Key words:** Parkinson's disease – drugs - adverse effects - treatment

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### INTRODUCTION

Parkinson's disease (PD) is a slowly progressive, degenerative disorder of the substantia nigra of unknown aetiology. Clinically PD manifests as an akinetic-rigid syndrome with the main clinical features of tremor, rigidity, bradykinesia and postural instability.

Historically, the use of anticholinergics by Charcot was the first efficient treatment of Parkinson's disease. The real substitution treatment started in the sixties of the last century by administering levodopa. The detailed knowledge of the pharmacodynamics and pharmacokinetics enabled introduction of dopamine agonists, COMT inhibitors, MAO-B inhibitors and some other drugs.

While individual approach to treatment still is of utmost importance, evidence based recommendations (such as those of a joint task force of the European Federation of Neurological Societies (EFNS) and the Movement Disorder Society-European Section (MDS-ES)) tend to shape a

therapeutic approach to early (uncomplicated) and late (complicated) Parkinson's disease.

In all stages of Parkinson's disease levodopa is the most effective therapy. However, long term complications associated with the pulsatile delivery of levodopa develop in a few years: fluctuations in motor performance, psychosis and dyskinesias. Therefore, particularly in younger patients, treatment may be initiated with MAO B inhibitor, like selegiline or rasagiline, amantadine, anticholinergics and dopamine agonists. Levodopa is the most effective symptomatic drug and it can be delivered in a relatively non-pulsatile manner (combination of levodopa, decarboxylase inhibitor and COMT inhibitor, possibly also in a single tablet). On the other hand, selegiline, MAO-B inhibitor, anticholinergics and amantadine often induce psychosis and as elderly are more sensitive to this side effect and less prone to developing motor complications, levodopa may be a better choice for early Parkinson's disease in an elderly patient.

When motor complications emerge in a levodopa-naïve patient, we can increase the dopamine agonist dose, switch between dopamine agonists or add levodopa. In a patient on levodopa, the dose and/or the frequency of the drug can be increased, COMT inhibitor (Adler et al. 1998) can be added to levodopa or a dopamine agonist added. MAO-B inhibitors, amantadine and anticholinergics should be added if not already part of management. When unpredictable offs and dyskinesia prevail, a continuous dopaminergic stimulation (apomorphine subcutaneous or levodopa (Duo-dopa) enteral infusions) or deep brain stimulation may be considered (Burchiel et al. 1999).

Obviously, antiparkinsonian treatment is a very dynamic, with potentially serious adverse effects and drug-related complications. On the other hand, the area is becoming a luring and inviting field for pharmaceutical industry. Sometimes drugs were made 'bad guys' as the knowledge and experience had expanded. Such was the case with anticholinergics and pergolide. Sometimes the research conclusions were wrong and unnecessarily induced fear of the drug: For example, a prematurely stopped randomised trial reported a 50% increase in mortality in subjects treated with selegiline combined with levodopa when compared with subjects treated with levodopa alone. But sometimes a war behind the scenes of pharmaceutical companies did help to shape attitudes and prejudices against a drug (the case of tolcapone).

### **Anticholinergics and cognition**

Anticholinergics were the first rational drugs for Parkinson's disease, used already by Charcot. There is a widespread belief that they are particularly efficient for tremor. Anticholinergics act by (1) correcting the disequilibrium between striatal dopamine and acetylcholine activity via a specific block of muscarinic receptors and (2) by blocking dopamine uptake in central dopaminergic neurons (bentropine). It seems that anticholinergics have a limited role in PD and the evidence for a special effect on tremor is inconclusive ('Management of PD' 2002; Katzenschlager et al. 2002).

However, the clinical use of anticholinergics has been severely limited particularly in elderly population. Although the most common side effects are blurred vision, urinary retention, nausea, constipation and dry mouth, it is impaired mental function which can be the most deleterious in elderly. Anticholinergics can acutely uncover dementia. If dementia is present, anticholinergics are strictly contraindicated. Of cognitive functions, it is mainly immediate memory and memory acquisition that suffers the most (van Herwaarden et al. 1993). Sedation, delirium and hallucinations are also well documented central side effects. Most of them resolve after the withdrawal of the drug, although dementia may persist.

As 30% of patients with Parkinson's disease suffer from dementia, anticholinergics should be used with an utmost caution in parkinsonians, particularly in elderly. Regular cognitive testing and focused history taking is important in these patients.

### **Selegiline and mortality**

Selegiline is also a relatively old drug, used already by Birkmayer. Selegiline inhibits the action of monoamine oxidase isoenzyme type B (MAO-B) thus preventing the breakdown of dopamine and increasing the available amount of this neurotransmitter.

An important UK study by Parkinson's Disease Research Group in the mid-nineties compared the effects of levodopa, selegiline and bromocriptine. The trial began in 1985 following earlier indications of a beneficial effect of selegiline. It included 822 patients with early Parkinson's disease randomised into one of three treatment arms: levodopa and dopa decarboxylase inhibitor (arm 1), levodopa and dopa decarboxylase inhibitor combined with selegiline (arm 2), and bromocriptine (arm 3). (Parkinson's Disease Research Group 1993) A pre-planned interim analysis in December 1994 revealed a significant difference in mortality between arms 1 and 2, and the group decided to stop treating patients with selegiline and to publish these results. There was an average of 5.6 years follow up, and the mortality hazard ratio comparing arm 2 with

arm 1 was 1.57 (95% confidence interval 1.07 to 2.31) after adjustment for age, sex, level of disability before treatment, duration of Parkinson's disease, and year of entry to the trial (Lees et al. 1995). However, concerns that the combination of selegiline and levodopa increase mortality rates in patients with early, mild Parkinson's disease (Ben Shlomo et al. 1998) have been rejected on the basis of a large meta-analysis (Olanow et al. 1998).

Selegiline has since been widely used in symptomatic treatment of Parkinson's disease and with less conviction as a potential neuroprotective substance. New MAO-B have emerged, of which rasagiline's possible disease modifying effect is currently one of the hot topics among movement disorder experts.

### COMT inhibitors and liver toxicity

One of the most vilified drugs in the nineties was tolcapone, a COMT inhibitor. Catechol-O-methyltransferase (COMT) inhibitors reduce the metabolism of levodopa, extending its plasma half-life and prolonging the action of each levodopa dose. There were two COMT inhibitors in nineties: entacapone and tolcapone, of which the latter seemed to be more potent. None of them caused hepatotoxicity in preclinical toxicity studies. However, in clinical trials of tolcapone, liver chemistry tests were elevated more than 3 times above the upper limit of normal in approximately 1% of patients who took the 100 mg dose and in approximately 3% of patients who took the 200 mg dose. These observations led to the recommendation that periodic monitoring of liver function be performed. Post-marketing surveillance studies noted 3 instances of acute liver failure with death after 60.000 patients had received tolcapone for a total of 40.000 patient years. For this reason, the drug was withdrawn from the market in Europe and Canada, and a black box warning issued in the USA. The drug is doing a cautious return in the last few years. The European Agency for the Evaluation of Medicinal Products (EMA) lifted the suspension of tolcapone for use in patients on levodopa who failed to respond to other COMT inhibitors, but imposed strict safety restrictions (EMA, 2004). Tolcapone can only be prescribed

by an expert in the field, starting with a recommended daily dose of 100 mg three times daily. Fortnightly blood tests for liver function are mandatory in the first year, at four weekly intervals for the next 6 months and, subsequently, every 8 weeks.

### Dopamine agonists and ...

Dopamine agonists are widely used in treatment of Parkinson's disease, particularly in younger patients. Dopamine agonists produce symptomatic antiparkinsonian effect via the shared D2-like receptor agonistic activity. The D2 effect largely explains also most common adverse effects of the drugs: peripheral (nausea, vomiting), cardiovascular (orthostatic hypotension) and neuropsychiatric (somnolence, psychosis and hallucinations). However, recently some specific complications are linked to the use of dopamine agonists.

### .... dopamine dysregulation syndrome

On the internet ([www.JimSokolove.com](http://www.JimSokolove.com)), one can read the following warning:

*“Have you Been Harmed by Requip? If you or your loved one has developed habit of compulsive or addictive gambling or suffered any other serious side effect after taking anti-Parkinson's Disease drug Requip, please fill out the form or call us at 1-800-275-0192 for an immediate response & Free Case Evaluation regarding your rights and information about compensation for injuries.”*

Use of the dopamine agonists (not only Requip!) and, less often levodopa, has been linked to the development of severe impulse control disorders, including compulsive or addictive gambling. Impulse control disorders are psychological conditions characterized by the inability to resist the impulse to perform an action that is harmful to the patients or others. Pathological gambling represents just a part of the spectrum in a newly described syndrome, labeled as hedonistic homeostatic dysregulation and dopamine dysregulation syndrome (Evans and Lees 2004). This is a neuropsychological behavioural disorder associated with dopamine

replacement drugs misuse and addiction. The disorder typically develops in male patients with early onset Parkinson's disease. One of the first warnings occurs when the patient starts taking increasing quantities of dopaminergic drugs, despite worsening of drug induced dyskinesia. He soon develops a cyclical mood disorder with hypomania or manic psychosis. Some patients develop punding. Punding is a term that was coined originally to describe complex prolonged, purposeless, and stereotyped behaviour in chronic amphetamine users, phenomenologically distinct from both obsessive-compulsive disorder and mania. The disorder is usually severe, leading to profound impairment of social and occupational functioning. Tolerance develops to mood elevating effects of dopaminergic drugs and an unpleasant affective withdrawal state occurs when the drug is withdrawn or doses decreased.

### ... sleep attacks

Over recent years there have been reports about sudden sleep attacks associated with dopamine agonists, often occurring without warning. 6.6% of patients on dopamine agonists have sleep episodes which were described to be of two types: sleep attacks and sleep episodes (Homan et al 2002). Sleep attacks means falling asleep suddenly, without warning signs and waking up a few minutes later. Sleep episodes are characterized by prodromal signs of tiredness followed by a slow and irresistible dosing off, with sleep lasting about 1 hour. However, some question the term sleep attacks, because sleep episodes without antecedent sedation are not known to occur under physiologic or pathologic conditions. An alternative explanation may be that these episodes reflect a combination of somnolence related to the sleep disturbances (often present in PD), and the propensity of dopaminergic drugs to induce dose-related sedation. Review of 20 publications, involving 124 patients, showed that it can occur with any dopamine agonist (Homan et al 2002). Other studies show that dopamine agonists differ in sedative effects, with pramipexole, presenting one of the largest numbers of event reports, on one side, and piribedil with the least

reports on the other side of the spectrum. Pramipexole is an  $\alpha_2$ -adrenergic presynaptic receptor agonist and decreases the noradrenergic pathway and consequently vigilance. Piribedil is an  $\alpha_2$ -adrenergic presynaptic receptor antagonist which raises noradrenergic activity and vigilance. Thus, the mechanism and frequency of this side effect remains controversial (Horne 2002), but the patients which take dopamine agonists should be warned about possible sleepiness, particularly if driving.

### ... restrictive valvular heart disease

Dopamine agonists which were used for the treatment of PD in the last thirty years can be divided into ergot derivatives (bromocriptine, cabergoline, dihydroergocryptine, lisuride and pergolide) and non-ergot derivatives (apomorphine, piribedil, pramipexole, ropinirole and rotigotine). It was clearly shown that a rare, but potentially dangerous risk of pulmonary and retroperitoneal fibrosis and valvular heart fibrosis as well as erythromelalgia, and Raynaud's-like phenomena is greater with ergot than with non-ergot dopamine agonists (Van Camp et al, 2004). At this moment, pergolide is only used as a second-line alternative option, when no other dopamine agonist provided an efficient improvement. X-ray should be promptly done at any suspicion of pleural fibrosis and ECG should be done if the ergot derivative has to be increased to its highest dosage in the case of a parkinsonian patient with a history or suspicion of coronary disease.

## CONCLUSION

Although some of the antiparkinsonian drugs have caused considerable concern and controversies and were regarded at certain points as the 'bad guys' of Parkinson's disease pharmacological armamentarium (e.g. anticholinergics, selegiline, tolcapone, dopamine agonists) they retain an important part in the spectrum of PD treatment. However, as our knowledge about possible adverse effects increases, we are becoming more cautious in the use of these once classical drugs.

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