

## Mental and Cognitive Disturbances in Parkinson's Disease

a report by

**Jaime Kulisevsky***Director, Movement Disorders Unit, Neurology Department, Sant Pau Hospital, Autonomous University of Barcelona*

DOI:10.17925/ENR.2006.00.02.52



Jaime Kulisevsky is Director of the Movement Disorders Unit in the Department of Neurology, Sant Pau Hospital, Autonomous University of Barcelona, Spain. Dr Kulisevsky is co-director of the Functional Neurosurgery Program for Parkinson's Disease at Sant Pau Hospital and Coordinator of the postgraduate magister 'Neuropsychological Diagnosis and Rehabilitation' at the Autonomous University of Barcelona. His main research and clinical interests involve the diagnosis and treatment of Parkinson's disease and other movement disorders, on which he has published numerous papers and acted as a reviewer on various scientific journals. He has been the recipient of several public research grants. A particular research interest has been the cognitive and behavioral consequences of basal ganglia dysfunction and the impact of antiparkinsonian treatment on cognition in Parkinson's disease.

Parkinson's disease (PD) is a progressive disorder of dopamine depletion involving multiple motor and non-motor circuits of the basal ganglia. Although the cardinal features of the disease are characteristically motor in nature (resting tremor, bradykinesia, rigidity and postural instability), changes in cognition, mood and emotion are common. Pathologically, it is characterised by fibrillar alpha-synuclein inclusions, known as Lewy bodies, in the pigmented neurons of the substantia nigra, associated with progressive degeneration of the nigrostriatal pathway, causing malfunctioning of the motor structures of the basal ganglia. Additional malfunctioning of the complex fronto-subcortical circuits of the basal ganglia in PD is almost invariably associated with relatively subtle 'dysexecutive' cognitive impairment reminiscent of frontal lobe lesions. This type of cognitive impairment in PD is variably associated to dopamine depletion in the ventral and dorsal striatum and in the dorsolateral prefrontal lobe, arising from additional degeneration of dopamine neurons in the ventral tegmental area (VTA) (area A-10) of the midbrain. Besides subtle cognitive deficits, epidemiological studies have shown that dementia associated to PD (PDD), which was once thought to be rare, may eventually develop in up to 75% of patients with PD. Progress in understanding the core components of Lewy bodies and alpha-synuclein staining lead to pathological studies evidencing that PDD is variably linked with cortical Lewy body topography and density. Accordingly, recent studies also indicate that degeneration of the midbrain dopaminergic neurons is only a part of PD and that alpha-synuclein pathologies accumulate throughout the central nervous system in areas that also undergo progressive neurodegeneration, leading to clinical symptoms that go far beyond motor parkinsonism. These include abnormalities in the regulation of mood, alterations in personality, impairments in olfactory discrimination and identification, impaired colour vision discrimination, decreased autonomic function and rapid eye movement (REM) sleep behaviour disorder.

When PD is clinically diagnosed, degeneration of dopaminergic neurons involves motor structures and also structures of the limbic system, affecting

dopaminergic cognitive, learning and reward mechanisms that can lead to subtle cognitive impairment, anhedonia, loss of motivation and apathy. With the progression of the disease, further involvement of other neuronal circuits such as noradrenergic, serotonergic and cholinergic, and the influence of non-physiological dopaminergic replacement may contribute to the variable presentation of other mental symptoms such as anxiety, depression, dementia and psychosis. Dopamine replacement therapy (DRT) with levodopa and other dopaminergic agents is a widely used and effective treatment for the motor symptoms of PD and, at least in the initial stages of the disease, has been shown to also benefit mood and certain cognitive functions. However, in chronically treated patients, DRT was variably associated to subtle cognitive impairment and to disabling behavioural side effects such as psychosis, hypersexuality, addiction, pathological gambling and punding. Dopaminergic-related neuropsychiatric problems in PD patients may be mild and under-recognised, or combined with premorbid personality traits can produce a complex and distressing clinical picture. With the progression of the disease, the behavioural and cognitive manifestations of PD are often more disabling than its motor complications.

Overall, PD should be viewed nowadays as a complex disorder, characterised by motor signs and by a broad and challenging range of neurological and psychiatric symptoms. This article highlights some of these aspects that emerge as the most difficult challenges of advanced disease, often limiting effective treatment of motor symptoms and leading to increased disability, worse quality of life, poorer outcomes and caregiver distress.

### Neuropsychiatric Symptoms in Parkinson's Disease and Parkinson's Disease Dementia

A wide variety of neuropsychiatric symptoms have been reported in PD. Using the neuropsychiatric inventory (NPI) – a highly structured, carer-based interview with questions for delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability and abnormal motor output –

the authors recently surveyed the overall rate of psychiatric symptoms in a community-dwelling population of 1351 consecutive non-demented PD patients. At least one psychiatric symptom was reported in 68% of the sample. The most common symptoms were apathy (48%), irritability (23%), anxiety (22%), depression (17%) and hallucinations (17%). Fifty per cent of these non-demented PD patients had scores ranging from possible (22%) to probable (28%) depression in a depression scale. Executive impairment (as measured by verbal fluency tasks including semantic, phonemic and alternating conditions) was found in 41%; and excessive daytime somnolence was found in 26% of the patients. Psychiatric symptoms, executive dysfunction and excessive daytime somnolence were significantly more common among patients with longer ( $\geq 7$  years) duration and greater stage of the disease. These findings confirm the existence of a wide spectrum of psychiatric symptoms in non-demented PD patients that increase in frequency with longer duration of the disease and partially relate to executive dysfunction. Neuropsychiatric symptoms seem even more common in PDD. Among 537 patients with PDD drawn from an international multicentre clinical trial of rivastigmine, 89% of the patients presented at least one symptom on the NPI, 77% had two or more symptoms and 64% had at least one symptom with a score  $\geq 4$ . The most common symptoms were depression (58%), apathy (54%), anxiety (49%) and hallucinations (44%). Patients with more severe dementia and advanced PD had more neuropsychiatric symptoms. While in the study of non-demented PD patients, caregivers rated distress caused by neuropsychiatric symptoms as predominantly mild, nearly 60% of the caregivers of PDD patients reported at least one NPI symptom to be of at least moderate to severe distress.

### Mild Cognitive Impairment in Parkinson's Disease

Compelling evidence indicates that motor symptoms typical of PD are also accompanied by a characteristic pattern of neuropsychological impairment. Subtle but widespread cognitive impairment appears even in the absence of clinically apparent cognitive decline. Many of the deficits are reminiscent but not identical to those observed in patients with lesions of the prefrontal cortex (failure in executive function that involves skills required for anticipation, planning, initiation and monitoring of goal-directed behaviours). Cognitive functions depending on the frontal cortex, such as the ability to suppress unwanted behaviour – response inhibition – and to learn complex feedback – probabilistic learning – play critical roles in activities of daily living. The most salient features of the cognitive deficits are related to alterations of visuospatial processes, difficulties in

shifting conceptual sets and difficulties in maintaining mental sets. Patients can thus be considered to exhibit a lack of mental flexibility, with failure to modulate frontal activation with increased task demands, which illustrates marked alteration of frontocortical processes.

The midbrain dopamine system plays an important role in particular types of learning, memory and executive functions that are frequently impaired in PD patients. Mild cognitive deficits secondary to dopamine deficiency in PD preferentially impairs performance in memory-guided tasks and not in those guided by external stimuli. Working memory is a mnemonic process especially vulnerable to dopamine loss. Neuroimaging studies support that both deficit of dopamine on the basal ganglia and impaired dopaminergic regulation of the mesolimbocortical dopamine system are probably involved in these alterations. Diminished dopamine in the basal ganglia – associated with impoverished inhibition of irrelevant stimuli for a particular task – and diminished dopamine in the prefrontal cortex – associated with a lack of 'focusing effect' for the task – results at behavioural level in an executive burden, with patients always performing as if they had a secondary task demand.

Although dopaminergic neurons may not be integral parts of the neuronal networks involved in the production of all the cognitive functions known to be altered in PD, it appears that dopamine neurons may regulate such behavioural processes, as they do for motor and limbic aspects of behaviour. The role of noradrenaline, serotonin and acetylcholine deficits in cognition in non-demented PD patients is less characterised. Impairment of cognitive functions in the early stages of PD, when the neurodegenerative process is thought to be mostly limited to the dopaminergic neurons, supports that dopaminergic neurons play a key role in controlling cognitive processes in PD.

A large cohort study showed that sub-groups of PD patients based on cognitive ability might be identifiable even in the early stages of disease, which may reflect regional differences in the underlying neuropathological processes. From 36% of newly-diagnosed patients showing some degree of cognitive impairment, 30% had a specific frontostriatal type of cognitive deficit, 21% had a specific temporal deficit and 37% had global deficit in cognitive functioning. The pattern of cognitive deficits seen among these patients may reflect regional differences in the underlying neuropathological processes and, probably, different risks of developing later dementia.

### Treatment of Cognitive Impairment in Parkinson's Disease

There is no specific treatment for the disexecutive

syndrome of non-demented PD patients. Levodopa, the most efficacious treatment for the motor symptoms, may have different effects according to the stage of the disease and the patients' motor response (stable or fluctuating) with important consequences on cognitive performance. Consequent with the 'Inverted-U'-shape response-curve of dopamine as a neuromodulator and the narrow range of dopaminergic stimulation for optimal cortical efficiency (Goldman), cognitive effects depend both on the level of dopamine depletion and the ability to buffer the intermittent acute excess of dopaminergic stimulation in different parts of the basal ganglia and prefrontal cortex. Thus, contrasting and dissociable effects of dopaminergic stimulation are observed across the evolution of PD.

In recently diagnosed patients with PD exhibiting relatively subtle cognitive impairment, dopaminergic replacement improves motor symptoms and may also improve cognitive performance. Significant improvement can be observed in tests assessing learning and long-term verbal and visual memory, visuospatial abilities and various frontal tasks. Nevertheless, improvement is not enough to reach the range of normal controls. In the long-term (18 months), improvement declines and loses significance after two-year follow-up. The incomplete improvement – implicating mainly frontal tasks, but also tasks tapping other cognitive domains such as memory or visuoconstructive abilities – and the ensuing motor decline suggests that dopaminergic replacement does not compensate for all of the cognitive deficits of patients with PD and that other (non-dopaminergic) factors intervene.

In advanced PD patients under chronic treatment but still showing a stable response to oral levodopa, the possible cognitive gain associated to initial dopamine replacement has already been produced and their presynaptic dopaminergic system still has the capacity to buffer the excess of dopamine formed from doses of levodopa required to maintain their motor gain. Then, except for reducing the response time in some tests, acute challenge with levodopa in stable patients tends to produce little, if any, modification in the accuracy in tasks covering a wide range of cognitive domains.

Contrarily, in PD patients exhibiting the wearing-off response, further increases in dopaminergic stimulation (linked to the hypermetabolic dopaminergic state associated with the wearing-off response) may cause defective function of the dorsal prefrontal cortex, resulting in transitory cognitive deterioration in coincidence with the peak of levodopa plasma levels.

Thus, enhancement and impairment of cognitive function with dopaminergic treatment in non-


demented PD patients is incomplete and task-specific, suggesting the need to integrate the above dopamine facts with other neurotransmitter systems deficits in PD.

In addition to transient cognitive oscillations, subclinical mood swings may be observed in PD patients with the wearing-off response. Significant mood changes – with more euphoric ratings at high plasma levodopa levels – not observed in patients with stable response to levodopa, appears more related to the rapid increase in levodopa plasma levels than to the motor improvement associated to levodopa dosing. Contrarily, a slower rise in levodopa plasma levels with comparable motor improvement obtained with controlled-release levodopa was not associated with affective swings. The differential mood-response induced by each type of levodopa in wearing-off patients most likely reflects differences in the velocity of extrasynaptic dopaminergic rise, with rapid rising favouring vulnerability to emotional swings. The more acute variations in central dopamine concentration induced by standard levodopa acting on abnormally regulated neural systems modulating mood might induce transient euphoric symptoms at high and transient depressive symptoms at low levodopa plasma levels. Marked functional changes in fronto-limbic circuits may underlie the susceptibility of some motor fluctuating patients to present with clinically relevant levodopa-related affective swings.

#### **Treatment of Cognitive Symptoms in Patients with Dementia Associated with Parkinson's Disease**

The loss of cholinergic innervation seen in PDD suggests a role for cholinesterase inhibitors. A growing literature suggests that these drugs improve cognitive function in patients who have PDD without worsening the motor symptoms of the disease. Improvement of cognitive symptoms and activities of daily living is only modest. Notably, these studies also indicate that cholinesterase inhibitors may reduce neuropsychiatric symptoms in PDD, particularly hallucinations and delusions. The efficacy and safety of rivastigmine, an inhibitor of acetylcholinesterase and butyrylcholinesterase, were demonstrated in a 24-week double-blind placebo-controlled trial with a large cohort of PDD patients. In an active treatment extension of this study for up to 48 weeks, placebo patients switching to rivastigmine experienced a mean cognitive improvement similar to that of the original rivastigmine group during the double-blind trial. Adverse events in both trials were mainly associated with the cholinergic activity of rivastigmine. ■

*A version of this article containing references can be found in the Reference Section on the website supporting this briefing ([www.touchneurology.com](http://www.touchneurology.com)).*



An adjunct therapy to levodopa/carbidopa or levodopa/benserazide in the treatment of idiopathic Parkinson's disease in patients with motor fluctuations who failed to respond to or are intolerant of other COMT inhibitors

## KEEP THEM "ON" LONGER WITH TASMAR

**TASMAR improves symptom control with more "ON" time**

- Increases "ON" time 1.7–2.9 hours and decreases "OFF" time 1.6–3.2 hours per 16-hour waking day<sup>1-4</sup>
- Patients experienced a 71% to 91% improvement in symptom severity and "wearing off" effect at 3 months<sup>2</sup>
- Reduces levodopa daily dose by up to 29% due to a significant increase of levodopa bioavailability<sup>1</sup>

Liver monitoring is essential for patients taking TASMAR.

For further information, please see the TASMAR abbreviated prescribing information on the reverse side.

 **TASMAR**<sup>®</sup>  
(tolcapone) *tablets*  
100mg  
Longer-lasting "ON" time



**REFERENCES:** 1. Adler CH, Singer C, O'Brien C, et al, for the Tolcapone Fluctuator Study Group III. Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson disease treated with levodopa-carbidopa. *Arch Neurol.* 1998;55:1089-1095. 2. Rajput AH, Martin W, Saint-Hilaire M-H, et al. Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind, placebo-controlled, multicenter trial. *Neurology.* 1997;49:1066-1071. 3. Baas H, Beiske AG, Ghika J, et al. Catechol-O-methyltransferase inhibition with tolcapone reduces the "wearing off" phenomenon and levodopa requirements in fluctuating parkinsonian patients. *J Neurol Neurosurg Psychiatry.* 1997;63:421-428. 4. TASMAR Complete Prescribing Information (US).

#### **TASMAR abbreviated prescribing information**

##### **TASMAR® 100 mg film-coated tablets.**

**Active substance:** Tolcapone.

**Composition:** 1 film-coated tablet contains 100 mg Tolcapone. Excipients: Tablet core: calcium hydrogen phosphate (anhydrous), microcrystalline cellulose, polyvidone (K30), sodium starch glycolate, lactose monohydrate, talc, magnesium stearate; film-coating: hypromellose, talc, yellow iron oxide (E172), ethyl cellulose, titanium dioxide (E171), triacetin, sodium lauryl sulphate.

**Indications:** Parkinson's disease. Use TASMAR only together with levodopa/benserazide or levodopa/carbidopa in patients with motor fluctuations who failed to respond to or are intolerant of other COMT inhibitors. Because of the risk of potential fatal, acute liver injury, Tasmar should not be considered as a first-line adjunct therapy to levodopa/benserazide or levodopa/carbidopa.

**Posology:** 100 mg three times daily, exceptionally increase to 200 mg three times daily. **Special warnings and precautions:** Treatment should be started only by physicians who are experienced in the treatment of advanced Parkinson's disease. All of the risks must be explained to the patient.

**If no substantial clinical benefit is seen within 3 weeks, treatment with TASMAR should be discontinued.**

**Liver function tests:** If liver function tests are abnormal or if there are signs of impaired liver function Tasmar should not be prescribed. Liver function should be monitored every 2 weeks for the first year of treatment, then every 4 weeks during the following 6 months and every 8 weeks thereafter. For increased dosage to 200 mg tid, liver monitoring should take place before the increase and then re-initiate testing of aforementioned sequence. If the ALT and/or the AST levels exceed the upper limit of the normal range or if symptoms or signs suggest the development of liver failure (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, pruritus and right upper quadrant tenderness), Tasmar should be discontinued immediately.

**Neuroleptic malignant syndrome (NMS)** tends to appear after stopping or discontinuing Tasmar. Therefore, if symptoms (rigidity, mental status changes, elevated temperature) occur after discontinuing Tasmar, physicians should consider increasing the patient's levodopa dose. Tasmar should be immediately discontinued and the patient followed up closely.

**Adjustment of levodopa during treatment with Tasmar:** Patients may require a reduction (average 30%) in their levodopa dose.

**Adjustment of levodopa when discontinuing Tasmar:** Levodopa dosage may have to be increased most likely within 1-2 days.

#### **Contraindications:**

Tasmar is contraindicated in patients with:

- Evidence of liver disease or increased liver enzymes.
- Severe dyskinesia.
- A previous history of Neuroleptic Malignant Syndrome Symptom Complex (NMS) and/or non-traumatic Rhabdomyolysis or Hyperthermia.
- Hypersensitivity to tolcapone or any of its other ingredients.
- Phaeochromocytoma.

**Undesirable effects:** Most commonly observed adverse events are: Increased dyskinesia, nausea, vomiting, abdominal pain, syncope, orthostatic complaints, constipation, sleep disorders, somnolence, diarrhoea, hallucinations, liver function disorders. Rare cases of hepatocellular injury resulting in death have been reported. Very rarely, patients develop Neuroleptic Malignant Syndrome Complex following reduction or discontinuation of Tasmar and following introduction of Tasmar when other dopaminergic medications were significantly reduced. Rhabdomyolysis, secondary to NMS or severe dyskinesia, has been observed.

**Overdose:** Possible symptoms: nausea, vomiting, dizziness, were observed particularly in combination with levodopa. Hospitalisation is advised.

#### **Pregnancy and lactation:**

**Pregnancy** — In rats and rabbits, embryo-foetal toxicity was observed therefore, Tasmar should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

**Lactation** — In animal studies, tolcapone was excreted into maternal milk. The safety of tolcapone in infants is unknown; therefore, women should not breast-feed during treatment with Tasmar.

#### **Effect on the ability to drive and operate machines:**

Patients should be advised that their ability to drive and operate machines may be compromised due to their Parkinson's disease symptoms.

**MA Holder:** Valeant Pharmaceuticals Ltd., Cedarwood, Chineham Business Park, Crockford Lane, Basingstoke, Hampshire, RG24 8WD, UK.

**Prescription only medicine:** Information as of August 2006.



Cedarwood, Chineham Business Park  
Crockford Lane, Basingstoke, Hampshire  
RG24 8WD, United Kingdom  
©2006 Valeant Pharmaceuticals Ltd. 800-031