The co-existence of α-synuclein, β-amyloid plaque and tau aggregates has been shown to worsen cognitive impairment in Parkinson’s disease. Mesolimbic and mesocortical dopaminergic deficits are associated with cognitive dysfunction in Parkinson’s disease. However, cognitive deficits do not respond well to dopaminergic treatment, suggesting that other non-dopaminergic systems may contribute to cognitive impairment in Parkinson’s disease. Cortical and subcortical cholinergic dysfunction can occur in patients with Parkinson’s disease dementia and is usually greater in patients with dementia occurring later in the disease course.

Noradrenergic and serotonergic systems may also be involved in the development of cognitive deficits in Parkinson’s disease since both atomoxetine and citalopram have been shown to improve executive deficits in Parkinson’s disease. Postmortem studies have demonstrated that mitochondrial complex 1 activity and mitochondrial DNA levels are decreased in the brain of Parkinson’s disease dementia patients.

Neuroinflammation and in particular increased microglial activation contributes to neuronal loss in Parkinson’s disease dementia.

In conclusion, alongside α-synuclein, tau and amyloid pathologies, several other mechanisms, including different neurotransmitter systems, neuroinflammation, and mitochondrial dysfunction, are likely to contribute to cognitive decline in Parkinson’s disease.

REFERRAL
Patients with Parkinson’s disease who present with symptoms of cognitive decline, behavioural changes or psychotic symptoms should be referred for further investigation.

Identifying these symptoms may require targeted questions during the interview, information from the caregivers, or the use of neuropsychiatric and cognitive assessment tools such as the Neuropsychiatric Inventory (NPI) and the Montreal Cognitive Assessment (MoCA) test. The self-reported Non-Motor Symptoms Questionnaire (NMSQ) is a valuable tool to screen for subjective cognitive impairment and has been recommended by NICE and Parkinson’s UK.

In a primary care setting, basic investigations should include routine haematology, biochemistry tests (electrolytes, calcium, glucose, renal and liver function), thyroid function tests, serum vitamin B12 and folate levels. A midstream urine test should be included in cases where delirium is suspected, while the need for a chest X-ray or ECG are determined by clinical presentation.

Parkinson’s disease patients with suspected cognitive impairment should then be referred to specialist movement disorders clinics. The differential diagnosis in such cases is broad and includes Parkinson’s disease MCI, Parkinson’s disease dementia, Lewy body dementia, delirium, other dementias, other psychiatric and medical conditions, substance misuse and side effects of medication, see tables 2 and 3, opposite.

The work-up of these patients should include detailed neuropsychological assessment, targeted physical examination, blood tests and neuroimaging studies and referral to a movement disorders clinic.

Once a diagnosis has been established, underlying causes should be addressed and the patient needs to be monitored closely over time.

Diagnosing Parkinson’s disease MCI or Parkinson’s disease dementia remains a challenge for clinicians from all specialties. Fluctuation in motor symptoms that interfere with daily activities, non-motor symptoms that affect cognitive function and neuropsychological assessments as well as medication already used need to be taken into consideration during the diagnostic process and before implementing targeted management strategies.

MANAGEMENT
Parkinson’s disease dementia is a progressive disease that could eventually lead to palliative care; thus evidence-based practice is critical in helping patients receive high quality care.

After ruling out other causes of cognitive impairment, GPs should refer the patient to secondary care. A thorough medication review should be carried out with a view to discontinuing any non-parkinsonian medications acting on the central nervous system (e.g. tricyclics), anticholinergic drugs (e.g. trihexyphenidyl), amantadine, and optimising dopaminergic treatment.

As yet, there are no pharmacological disease modifying therapies able to prevent or delay deterioration of cognitive impairment in Parkinson’s disease although some medications may ameliorate cognitive and behavioural symptoms. To date, randomised placebo-controlled trials