Med Clin (Barc). 2017;148(5):232–237

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Diagnosis and treatment

Treatment of cognitive impairment in Parkinson disease☆

Tratamiento del deterioro cognitivo en la enfermedad de Parkinson

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ARTICLE INFO

Article history:
Received 16 October 2016
Accepted 27 October 2016
Available online 24 March 2017

Introduction

Mild cognitive impairment (MCI) and dementia are common disorders in Parkinson's disease (PD). The prevalence of PD with dementia (PDD) is over 80% at 20 years of follow-up. This leads the patient to lose autonomy, with high impact on their and their relative's quality of life.[1]

PD-MCI (cognitive performance below normal for the patient's age and educational level, which remains independent for activities of daily living [ADL]) increases the risk of conversion to dementia.[2,3] It is an heterogeneous entity, in both number and type of cognitive domains involved (attention, executive function, memory, visuospatial function and language). Subsequent cortical deficits (visuospatial function and semantic verbal fluency) appear to increase the risk of dementia.[2,4,5]

Neuropathology and biochemistry of cognitive impairment in Parkinson's disease

One of the causes of cognitive symptoms is the deficits in monoaminergic systems. The progressive loss of striatal dopaminergic innervation, in addition to causing the classic motor signs, associates executive dysfunction (such as difficulties in planning, attention, etc.). The noradrenergic deficit might also have a role in design and learning disorders due to the degeneration of the locus coeruleus. Finally, the deficit of acetylcholine, a neurotransmitter of major relevance in CI, is extensive in PD and PDD, even higher than in AD, and is involved in maintaining attention (involving indirectly executive function), memory loss, deficit of visuospatial function and visual hallucinations.[6]

The presence of neocortical and limbic LCs is the most important pathological substrate in the development of PDD. The typical pathology of AD (beta-amyloid and neurofibrillary tangles) occurs in half of the cases and might be involved in an early onset of dementia.[6]

This paper will describe the existing studies in the treatment of CI, PD and will give a practical vision of its management.

Methods

A bibliographic review and a review of the registry of the National Institute of Health of the USA has been carried out (www.clinicaltrials.gov) on pharmacological and non-pharmacological treatment (deep brain stimulation and non-invasive treatments: physical activity, cognitive stimulation, repetitive transcranial magnetic stimulation and transcranial direct-current stimulation).

Results

General approach

In a patient with PD and CI, we will first rule out non-disease causes that may worsen or cause degeneration, including drug adverse effects, depression, cerebrovascular disease, systemic or metabolic disorders. We will carefully review the medication, mainly recent modifications, since some treatments with anticholinergic effect (amantadine, trihexyphenidyl or oxibutitin for urinary symptoms), benzodiazepines and dopaminergic agonists might be involved. We must rule out reversible causes of cognitive impairment by analyzing thyroid function, folic acid, and vitamin B12. An abrupt onset would also lead one to think of other causes of degeneration. In some cases, a brain MRI might be useful[7] (Table 1).

Once secondary causes have been ruled out, we will consider non-pharmacological measures such as cognitive therapy and

☆ Please cite this article as: Gasca-Salas C. Tratamiento del deterioro cognitivo en la enfermedad de Parkinson. Med Clin (Barc). 2017;148:232–237.

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Table 1
Strategy for the treatment of mild cognitive impairment and dementia in Parkinson's disease.

1. Cognitive evaluation and study of potential concomitant depression
2. Careful review of the medication and adjustment: anticholinergic drugs, dopaminergic agonists, benzodiazepines
3. Blood test: vitamin B12, folic acid and thyroid function. Assess if the study of other metabolic/systemic impairment is necessary. Rule out urinary tract infection in cognitive impairment and/or associated psychosis
4. Brain MRI: non-diagnostic but it may show brain atrophy and rule out associated vascular pathology
5. In Parkinson's disease dementia: start treatment with anticholinesterase inhibitors. If possible, rivastigmine in patches
6. Physical exercise on a regular basis and intellectual activity

physical exercise (they can also be used preventively) and we will assess a potential benefit of the pharmacological treatment.

Pharmacological and surgical treatment

Pharmacological treatment includes strategies based on neurotransmitter deficiency.

Dopaminergic therapies can improve, mainly at the onset of the disease in some patients, aspects of executive function (mental flexibility or working memory), which would depend on frontostriatal associative circuits. On the contrary, other aspects of the executive function may worsen caused by an overstimulation of a less denervated limbic and orbitofrontal circuit.[8] In dementia, the potential negative cognitive effects are more evident, which can induce more confusion and hasten or worsen hallucinations. Reducing these agents, or replacing by any other type (eg, dopaminergic agonist to levodopa/carbidopa) may lead to clinical improvement. However, even though levodopa/carbidopa is best tolerated, side effects may continue.[7]

Parkinson's disease dementia

Anticholinesterase inhibitors. In a 24-week double-blind, placebo-controlled study of 541 patients with mild-moderate dementia, rivastigmine efficacy wass proved in the clinical global impression scale (CGIS) and neuropsychologically. The most common side effects were nausea-vomiting and worsening of tremor.[9] Subsequent studies found that improvement occurred in all aspects of attention[10] and in the reduction of visual hallucinations, frequent in PPD. In longer studies, the improvement lasted up to week 48, but less effective, being safe at week 76.[11]

The results with donepezil have been contradictory. In a randomized, double-blind, placebo-controlled study of 550 patients with mild-to-moderate PPD no cognitive differences were reported in CGIS between patients taking 10, 5 mg or placebo after 24 weeks. However, both doses of donepezil were proved to be effective in tests of global cognition, attention and executive function (secondary endpoint).[12]

The rest of the studies have included small samples, which may explain the poor or lacking benefit. In a 10-week double-blind, placebo-controlled study in 14 patients, donepezil improved cognition slightly with good tolerance.[13] In another double-blind, cross-sectional study with 2 periods of 10 weeks separated by a wash-out time no improvement was reported in cognition (primary endpoint) but it was in the CGIS (secondary endpoint).[14] Finally, Leroi et al., in 16 subjects randomized to placebo or donepezil, observed very slight improvement in memory, without other differences at a cognitive level. Side effects were more frequent in the donepezil group, with mild to moderate intensity.[15]

Finally, a in study with galantamine in PDD, efficacy was reported in cognition, hallucinations, anxiety, apathy and sleep compared to placebo, but it included a small sample (41 patients) and despite being controlled it was an open study.[16]

These drugs are well tolerated, with a dropout rate by 10–31% and side effects similar to those described in AD. The most frequent are nausea-vomiting, followed by hypersalivation, rhinorrhea and tearing (15%), and to a lesser extent postural hypotension, falls and syncope (10%). In some patients in the active group of the clinical trials there was worsening of parkinsonian symptoms, particularly in tremor, but no impact on motor UPDRS and total UPDRS.[17] Adverse effects appear to be less frequent in those using the rivastigmine patches.

Due to potential cardiovascular effects (hypotension, bradycardia) and, as a consequence, risk of syncope and falls, in clinical practice some specialists include an ECG and blood pressure measurement prior to treatment to rule out hypotension or underlying cardiac abnormalities that contraindicate their use. In general terms, anticholinesterase inhibitors pose an acceptable risk with no specialized supervision.

The Movement Disorders Society (2011 and 2013) reviewed the effectiveness of these treatments and showed that rivastigmine is effective and clinically useful. However there is no sufficient evidence for donepezil and galantamine but they are potentially useful based on their effectiveness and approval outside PD[18] (Table 2). In a recent meta-analysis it was reported that, although with mild effect, anticholinesterase inhibitors are effective in PDD, both in cognition and in behavioral impairment and ADL.[17]

An abrupt withdrawal may worsen cognitive and psychiatric symptoms. Therefore, it is recommended that this treatment be maintained long-term in patients with good response.

Memantine. It is an N-methyl-D-aspartate receptor antagonist whose mechanism would normalize glutamatergic dysfunction. In a randomized, controlled, small size (n = 25) double-blind 22-week clinical trial in PDD, there were no differences between the active and control groups. However, after withdrawal of the medication, patients who received memantine showed a higher degree of impairment. Thus memantine was proved to be beneficial to some extent.[19] In a larger (n = 72) (randomized, controlled, double-blind) study that also included patients with LB dementia, there was a significant benefit in the CGIS in favor of the active group but no improvement in secondary endpoints: The Mini-Mental State Examination (MMSE) and the neuropsychiatric inventory.[20] In a more recent study in a larger PDD and LB dementia population (199 patients), there were no differences at week 24 in the CGIS in the PDD active treatment group, but there were differences in the LB dementia group.[21] However, in another study with 51 PDD or LB dementia patients, memantine was effective in cognitive tasks in both groups, with a medium-long effect size.[22] Finally, it is worth mentioning an effect of this drug on survival in PDD and LB dementia patients, suggesting a potential modifying effect of the disease.

Memantine is well tolerated and it rarely causes adverse effects (as in AD). Therefore it poses no safety concerns. We can conclude that memantine at most has mild beneficial effects on PDD, mainly in global cognition and behavioral symptoms, but the data are contradictory. Therefore, it is deemed potentially useful but it does not show sufficient evidence to be considered clinically useful.[18] (Table 2).

Active clinical trials. Of the clinical trials described at www.clinicaltrials.gov, there is only one controlled, randomized, double-blind clinical trial in PDD, the SYNAPSE. This phase-II trial evaluates SYN120 safety, tolerability and effectiveness, a dual 5-HT6/5-HT2A dual antagonist in PDD patients treated with a stable dose of anticholinesterase inhibitors. These receptors involved in cognitive, mood and psychosis processes are located in