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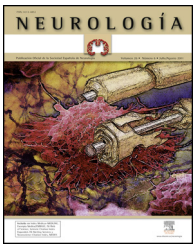

REVIEW ARTICLE

Dopaminergic agonists in Parkinson's disease☆

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Prolonged release;
Equivalence

Abstract
Background: Non-ergoline dopamine agonists (DA) are effective treatments for Parkinson's disease (PD). This review presents the pharmacology, evidence of efficacy and safety profile of pramipexole, ropinirole, and rotigotine, and practical recommendations are given regarding their use in clinical practice.
Results: Extended-release formulations of pramipexole and ropinirole and transdermal continuous delivery rotigotine patches are currently available; these may contribute to stabilising of plasma levels.

In early PD, the three drugs significantly improve disability scales, delay time to dyskinesia and allow a later introduction of levodopa. In late PD they reduced total 'off'-time, improved Unified Parkinson's Disease Rating Scale (UPDRS) in both 'on' and 'off' state and allowed a reduction in total levodopa dosage. A significant improvement in quality of life scales has also been demonstrated. Extended-release formulations have proved to be non-inferior to the immediate release formulations and are better tolerated (ropinirole). Despite a generally good safety profile, serious adverse events, such as impulse control disorder and sleep attacks, need to be routinely monitored. Although combination therapy has not been addressed in scientific literature, certain combinations, such as apomorphine and another DA, may be helpful. Switching from one DA to another is feasible and safe, although in the first days an overlap of dopaminergic side effects may occur. When treatment with DA is stopped abruptly, dopamine withdrawal

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syndrome may present. Suspending any DA, especially pramipexole, has been linked to onset of apathy, which may be severe.
Conclusions: New non-ergotine DAs are a valuable option for the treatment of both early and late PD. Despite their good safety profile, serious adverse effects may appear; these effects may have a pathoplastic effect on the course of PD and need to be monitored.

PALABRAS CLAVE
Agonistas dopaminérgicos;
Pramipexol;
Ropinirol;
Rotigotina;
Liberación prolongada;
Equivalencia

Agonistas dopaminérgicos en la enfermedad de Parkinson

Resumen
Introducción: Los agonistas dopaminérgicos no ergóticos (AD) son tratamientos útiles en la Enfermedad de Parkinson (EP). Revisamos la farmacología, el grado de evidencia en cuanto a eficacia y tolerabilidad de pramipexol, ropinirol y rotigotina, y proponemos algunas recomendaciones para su uso en la práctica clínica.
Desarrollo: En el momento actual se dispone de formas de liberación prolongada (LP) de pramipexol y ropinirol y de administración transdérmica de rotigotina, que contribuyen a una mayor estabilidad plasmática de los niveles del fármaco. En la EP inicial los tres fármacos mejoran de forma significativa las escalas de incapacidad de los pacientes, retrasan la aparición de discinesias y permiten retrasar la introducción de levodopa. En la EP avanzada reducen el tiempo *off*, mejoran la UPDRS en *on* y en *off* y permiten reducir la dosis total de levodopa. Además, los tres han sido capaces de inducir una mejoría significativa en las escalas de la calidad de vida relacionada con la salud. Las fórmulas de LP han demostrado la no inferioridad frente a las de liberación inmediata, e incluso una mejor tolerabilidad (ropinirol). A pesar de su buen perfil de seguridad, entre los efectos adversos graves cabe destacar el trastorno de control de impulsos, cuya aparición puede ser precoz, y los accesos de sueño (*sleep attacks*). Aunque la terapia combinada no ha sido estudiada específicamente, algunas asociaciones (como la de apomorfina y otros AD) pueden ser beneficiosas. El cambio de un AD a otro es factible de un día para otro, aunque en los primeros días puede haber una sumación de efectos adversos dopaminérgicos que debe tenerse en cuenta. La suspensión brusca del tratamiento con AD puede inducir un síndrome de deprivación dopaminérgica. La retirada de cualquier AD, en particular pramipexol, se ha asociado a aparición de apatía que puede ser grave.
Conclusiones: Los nuevos AD no ergóticos constituyen una opción válida de tratamiento de la EP tanto inicial como avanzada. A pesar de su buen perfil de tolerabilidad, no están exentos de efectos adversos graves, que pueden tener un efecto patoplástico en la EP y que deben monitorizarse.

Introduction

Levodopa remains the most effective symptomatic treatment for Parkinson's disease (PD). However, its relationship to the onset of motor complications (fluctuations and dyskinesia) places some limits on its use, especially in patients younger than 70 with mild PD symptoms. Dopaminergic agonists (DA) provide a safe and effective alternative to levodopa in younger patients and using these drugs is associated with a lower incidence of motor complications at the 5-year mark. They are effective both as monotherapy in early stages of the disease and in combination with levodopa in advanced PD. Ergot derivatives were the first DAs available, but use of these drugs is currently restricted due to risk of fibrotic valvular heart disease[1,2] and they should never be considered for first-line treatment.

Non-ergoline DAs may be administered orally (pramipexole and ropinirole), transdermally (rotigotine) or subcutaneously (apomorphine). Extended-release oral formulations allowing patients to take a single daily dose have recently been introduced. These formulations were developed in order to achieve more stable plasma drug concentrations, thereby minimising motor fluctuations as much as possible. These fluctuations are at least partially derived from oscillations in plasma drug concentrations.[2] Another DA, rotigotine, was recently designed for the same purpose; the first non-ergoline, transdermally delivered DA has an effectiveness and safety profile similar to those of other drugs in its class.

While the new DAs are not without severe adverse effects, particularly impulse control disorder (ICD), their effect on quality of life for PD patients has been unquestionably beneficial. They have also considerably widened the range of treatment strategies available to neurologists. In this review, we will use a practical approach to analyse pharmacological factors, adverse effects, and clinical utility of the three most widely used dopaminergic agonists in clinical practice (pramipexole, ropinirole, and rotigotine).

Pharmacokinetics and pharmacodynamics

Pramipexole

Pramipexole's chemical name is (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole. It is a potent D_2