

## **DOPAMINE AGONISTS ARE STILL FUNDAMENTAL IN THE TREATMENT OF PD : NO**

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In PD, dopaminergic neurons in the substantia nigra degenerate. Approximately 80% of dopamine in the striatum is lost before Parkinsonian symptoms occur. Levodopa treats these symptoms by crossing the blood brain barrier, entering neurons and being processed to dopamine which is then available for release in the synaptic cleft. However in advanced PD or with chronic use, patients develop motor complications. These include "wearing off" when doses of levodopa do not last as long, and dyskinesias which are excess involuntary movements thought to be due to overactivity of dopaminergic motor pathways in response to levodopa.

DA agonists are used as adjuvant therapy to levodopa as well as monotherapy in early PD to minimize motor complications. DA agonists stimulate DA receptors providing an antiparkinsonian effect. DA agonists can stimulate receptors regardless of the degenerative state of dopamine neurons provided receptors are still present and unchanged. These agents have diverse chemical properties and can be divided into two general classes: ergot and non-ergot agents. Some side effects are thought to be shared among all dopaminergic medications, while others may be class specific. Rare but serious adverse effects have been linked to DA agonists, including sleep attacks, cardiac valvulopathy and repetitive behaviors. The etiology of such events remains speculative and data is insufficient to know true prevalence and risk to a given patient. Thus, clinicians are left in a difficult situation as there is cause for concern, but insufficient information to make definitive recommendations.

One study explored the French Pharmacovigilance Database and found:

The numbers of ADRs by system organ class were compared using ropinirole as a reference. Diurnal somnolence was less frequently reported with all DAs when compared with ropinirole ( $P < 0.001$ ). Impulse control disorders (ICDs) were more frequently reported with pramipexole ( $P < 0.001$ ). Significant difference was found among DAs in the frequency of confusion or disorientation

( $P < 0.001$ ), nausea and vomiting ( $P < 0.05$ ), or edemas ( $P$

$< 0.001$ ). No difference among DAs was observed in the frequency of hallucination or arterial hypotension

ADR reports

( $P = 0.3$  and  $P = 0.1$ ). Pleural effusions were more frequently

reported with pergolide or bromocriptine ( $P < 0.001$ ). Somnolence or ICD reports were less frequent with levodopa, whereas confusion was more frequently reported. In summary, our data show significant differences in the kind of ADRs reported for each DA.

Orthostatic hypotension has been well known to occur especially at the time of initiation of DAs so much so that some authors have suggested careful medical supervision at such time.

Given the potential for side effects, it is difficult to promote DAs as primary modality of treatment for Parkinson disease at any stage or at any age.