

# DOPAMINE AGONIST WITHDRAWAL SYNDROME (DAWS) IN PARKINSON'S DISEASE PATIENTS TREATED WITH LEVODOPA-CARBIDOPA INTESTINAL GEL INFUSION ( LCIG) AND REVIEW OF THE LITERATURE.



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## Background

Dopamine agonist withdrawal syndrome (DAWS) is as a severe, stereotyped cluster of physical and psychological symptoms that correlate with dopamine agonists (DAs) taper in a dose-dependent manner. DAWS symptoms (including anxiety, panic attacks, dysphoria, depression, agitation, irritability, suicidal ideation, fatigue, orthostatic hypotension, nausea, vomiting, diaphoresis, generalized pain, and drug cravings) causes clinically significant distress or social/occupational dysfunction and are often refractory to levodopa.

## Objective

To describe Parkinson's Disease (PD) patients who developed DAWS correlated with rapid taper of DAs after Levodopa-Carbidopa Intestinal Gel infusion (LCIG) initiation, and to review the literature about patients affected by DAWS.

## Methods

Four cases developing DAWS symptoms after the rapid withdrawal of DAs consequent to LCIG introduction were described and we conducted a detailed Internet-based literature search on all available articles about DAWS.

## Results

Demographic and clinical features of our patients are ( Table 1) : age ( 60 ± 9.7 ); disease duration (13 years); motor complications duration (4 ± 0.7 years); apathy/depression after LCIG introduction latency to onset (2 ± 0.5 days); duration (4 ± 0.7 months). We unsuccessfully tried to manage these DAWS symptoms by increasing LCIG flow. Within 6 months, all patients spontaneously presented a slow but gradual improvement of DAWS symptoms, not requiring any further treatment strategy or LCIG discontinuation.

There are in literature 15 papers ( 9 of them are reviews) about DAWS in PD patients with impulse control disorders, and after deep brain stimulation, and LCIG. DAWS has been also described in patients with Restless legs syndrome . To the best of our knowledge 31 patients were described : 20 of them taked pramipexole, 9 of them ropinirole, 1 cabergoline and 1 pergolide. It is very interesting to notice that DAWS happened with the oral administration of DAs but DAWS was not observed by the transdermal formulation of DAs. ( Table 2).

## Conclusions

In keeping with DAWS literature, we have described the occurrence of DAWS symptoms in advanced PD patients after DAs withdrawal in LCIG highlighting the difficulty of distinguishing postoperative effects from drug withdrawal symptoms. Therefore we wish to draw attention of clinicians to the risk of developing DAWS in these patients.

Table 1. Demographic and clinical features of PD patients with DAWS symptoms before LCIG (Baseline) and at follow-up visit (two months after LCIG).

	Case 1	Case 2	Case 3	Case 4
Age	60	75	78	66
Gender	F	F	F	M
Disease duration	12	12	14	14
Motor complications duration (yrs)	4	6	3	6
MMSE	30/30	29/30	30/30	30/30
Baseline DA type	PRX	PRX	ROP	ROP
DA LEED	141	141	80	480
L-dopa LEED	800	450	800	1433
Total LEED	941	591	880	1913
UPDRS-III (med off)	43	26	35	43
UPDRS-III (med on)	15	13	16	9
UPDRS-IV	16	9	8	10
BDI-II	14	16	16	13
SAS	11	14	12	9
Previous history of DDS	yes	no	no	no
Follow-up visit after LCIG	1400	1100	1100	2000
Introduction L-dopa LEED (mg/daily)				
UPDRS-III (med off)	38	25	34	39
UPDRS-III (med on)	14	11	15	9
UPDRS-IV	8	5	4	5
BDI-II	29	28	26	34
SAS	29	30	26	32
Apathy/ depression after DAs	2	2	3	3
Withdrawal Latency to onset (days)				
Duration (months)	6	4	3	6
DAWS Management	Increase of LCIG flow (unsuccessful)	Increase of LCIG flow (unsuccessful)	Increase of LCIG flow (unsuccessful)	Increase of LCIG flow (unsuccessful) Rotigotine for 4 months
FU duration after resolution (months)	6	16	18	5
Other most relevant symptoms	Anhedonia, fatigue, generalized pain, insomnia, anxiety.	Anhedonia, fatigue, dizziness, orthostatic hypotension, diaphoresis	Anhedonia, anxiety, irritability, agitation, nausea, cramps.	Anhedonia, anxiety, nocturnal sleep disturbance, nausea, irritability, fatigue, diaphoresis, dizziness, generalized pain.

Abbreviations: PD, Parkinson's disease; DAWS, dopamine agonist withdrawal syndrome; LCIG: levodopa/carbidopa intestinal gel infusion; MMSE: mini-mental state examination, DA: dopamine agonist, PRX: pramipexole, ROP: ropinirole; LEED: levodopa equivalent daily dose (mg/day), UPDRS: Unified PD Rating Scale; BDI: Beck depression inventory; SAS: Starkstein Apathy Scale; FU: follow-up; DDS, dopamine dysregulation syndrome.

Table 2. Articles regarding DAWS in PD

Authors	Number of patients	Dopamine agonist tapered	Main non motor symptoms
Solla P., 2015 Parkinsonism and Related Disorders	4	Pramipexole (2) Ropinirole (2)	Apathy, depression, anhedonia
Todorova A., 2015 Basal Ganglia	1	Cabergoline	Depression, anxiety, hallucinations
Pondal M., 2013 Journal of Neurology, Neurosurgery and Psychiatry	13	Pergolide (1) Pramipexole (5) Ropinirole (7)	Anxiety,panic attacks, depression
Cunnington A.L., 2012 Parkinsonism and Related Disorders	7	Pramipexole	Panic attacks, depression, diaphoresis
Flament M., 2011 Neuropsychiatry Clin. Neuroscience	1	Pramipexole	Anxiety/depression disorder
Rabinak C.A., 2010 Archives of Neurology	5	Pramipexole	Anxiety, panic attacks, agoraphobia

## References

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