



## Dopamine agonist withdrawal syndrome associated factors: A retrospective chart review

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### ABSTRACT

Dopamine agonist withdrawal syndrome (DAWS) has been introduced to describe the constellation of symptoms resulting from reduction or suspension of dopamine agonist medications. In patients with Parkinson's disease (PD) the impact of DAWS can be significant in terms of distress and disability. Unfortunately, no standard treatment exists other than reintroduce the dopamine agonist even in the presence of adverse effects. Therefore, identification of vulnerable patients would be beneficial. Previous studies have linked DAWS with impulse control disorder behavior (ICD), higher dopamine agonist doses, and milder motor impairment in PD patients.

We conducted a retrospective chart review of PD patients treated with dopamine agonist. A total of 313 charts from January 2011 to December 2013 were reviewed, showing 126 patients who were discontinued from dopamine agonist. Twenty-one patients (16.8 %) fulfilled the diagnostic criteria for DAWS. Factors associated with the occurrence of DAWS were: (1) dose of dopamine agonist  $\geq 150$  mg expressed in levodopa equivalents daily dose (LEDD) ( $p = 0.018$ ), (2) impulse control disorder as an adverse effect to dopamine agonist ( $p = 0.002$ ), and (3) prior deep brain stimulation (DBS) ( $p = 0.049$ ). The probability of developing DAWS in the presence of all 3 identified factors was 92 %; presence of 2 factors raised the probability up to 70 %; the presence of one factor increased the probability up to 30 %. In the absence of these 3 factors the probability of developing DAWS was 3 %. Prospective studies are warranted to confirm these findings.

### 1. Background

Dopamine is a unique neurotransmitter. It is critical in the control of movement through the striatonigral pathway and also participates actively in the emotional reward mechanism through mesocorticolimbic circuits [1]. This underlies the complexity of motor and non-motor features in Parkinson disease (PD) [2]. Dopaminergic therapy e.g., levodopa and dopamine agonists, is the mainstay of treatment for PD. However, the activation of emotional reward pathways can lead to physical and psychological dependence (addiction), and subsequent risk of developing unpleasant symptoms when the substance is stopped or decreased (withdrawal syndrome) [3].

In the last 20 years, several types of addictive behaviors have been described in patients receiving dopaminergic therapy, especially dopamine agonist [4]. Compulsive shopping, excessive use of the internet, hypersexuality, gambling, punding, and binge eating are some of the common examples reported in the literature [5–7]. The term impulse control behavior disorder (ICD) has been used to designate these symptoms collectively [8]. It can be a significant source of burden for PD patients and caregivers [9], leading to abrupt and forced reduction or

discontinuation of dopamine agonist.

Dopamine agonist withdrawal syndrome (DAWS) has been described, as a frequently severe, stereotyped cluster of physical and psychological symptoms that correlates with dopamine agonist withdrawal in a dose dependent manner, causing clinically significant distress and social occupational dysfunction [10]. Symptoms include panic attacks, depression, diaphoresis, agitation, fatigue, pain, drug cravings, nausea and orthostatic hypotension [10].

This condition can affect as much as 19% of patients who taper or suspend the medication. Up to 50% will experience symptoms of withdrawal chronically (months or years). Previous studies have suggested a link between ICD, dopamine agonist dosage, and milder motor impairment in PD with the development of DAWS [10–12]. However, lower UPDRS scores have not been consistently associated with DAWS development [13]. Unfortunately, no standard treatment exists other than the reintroduction of dopamine agonist [12,14,15].

The aim of this study to identify potential risk factors associated with DAWS, and to design a probabilistic model that estimates the likelihood of developing the syndrome.

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## 2. Methods

We conducted a retrospective chart review of patients seen at Cleveland Clinic Center of Neurological Restoration. Patients carried PD diagnosis made by a fellowship trained movement disorders neurologist based on United Kingdom Parkinson Disease Society Brain Bank criteria and were treated with dopamine agonists. We obtained data through our Knowledge Program (KP). KP is a data capture initiative designed to harness routinely collected clinical information.

Data obtained included gender, ethnicity, age at time of dopamine agonist withdrawal, marital status, smoking history, substances abuse, PD duration, time of exposure to dopamine agonist, burden of dopaminergic treatment expressed in levodopa equivalents daily dose (LEDD), daily dose of dopamine agonist expressed in LEDD, Unified Parkinson Disease Rating Scale (UPDRS), Generalized Anxiety Disorder 7-item (GAD 7), Patient Health Questionnaire for depression (PHQ9), and history of deep brain stimulation (DBS) regardless the target, subthalamic nucleus (STN) or internus globus pallidus (GPi). Charts were reviewed to identify symptoms that could be considered a side effect of dopamine replacement therapy. These side effects were classified in 3 categories:

- ICD, e.g. hypersexual, gambling, eating, shopping, punding.
- Idiosyncratic dopamine side effects, e.g. leg swelling, weight gain, sleep attacks, skin reactions.
- General dopamine replacement therapy side effects, e.g. nausea/vomiting, orthostasis, cognitive loss, hallucinations/psychosis, sedation.

Patients who were withdrawn from dopamine were classified according to:

- Amount of dopamine agonist withdrawn: complete or partial.
- Speed of taper: <2 weeks, 2–4 weeks, and >4 weeks.
- DAWS: presence or absence of symptoms consistent with DAWS according to the definition proposed by Rabinak and Nirenberg: “severe, stereotyped cluster of physical and psychological symptoms that correlate with DA withdrawal in a dose-dependent manner, cause clinically significant distress or social/occupational dysfunction, are refractory to levodopa and other PD medications (and thus occur even in the on state), and cannot be accounted for by other clinical factors” [10].

The study was performed in accordance with Cleveland Clinic Institutional Review Board.

## 3. Statistics

Comparison between categorical variables was done using chi square ( $\chi^2$ ) and Fisher’s exact test. For continuous variables *t*-test and Mann Whitney were carried out. Statistical significance was defined as a *p* value < 0.05. After identifying risk factors bivariate logistical regression analysis with probabilistic model was performed. The statistical analysis was conducted with SPSS.

## 4. Results

A total of 313 charts were reviewed, 126 patients were discontinued from a dopamine agonist (40.2%) 98 of them (77.7%) because of adverse effects. The remaining 28 cases were due to other reasons including adjustment of regimen by other health providers, development of dyskinesias, DBS placement, or availability (Table 1). One out of these 126 was excluded because of loss of follow up. DAWS was diagnosed in 21(16.8%) patients.

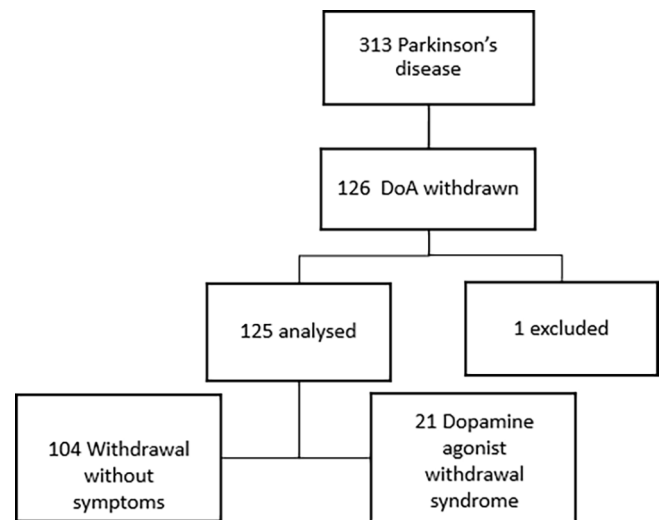
(Fig. 1) Demographics reflected similar characteristics between the DAWS and NO DAWS groups. No statistically significant difference in age, gender, marital status, race, or smoking history was documented

**Table 1**

Reasons for discontinuation of dopamine agonists.

Reason for Discontinuation of Dopamine Agonist		Number of Patients
adverse effects	ICD	23
	Idiosyncratic	25
	Generalized	63
other	Adjusted by other health provider	11
	DBS	6
	No availability of medication	4
	Loss of follow up	1
	Unknown	6

\*Some patients could be in more than one group.



**Fig. 1.** Patient flowchart.

(Table 2).

Regarding the analyzed factors, a higher dopamine agonist dose at the time of withdrawal was statistically significant for DAWS occurrence (*p* = 0.006). Particularly, doses greater than or equal to 150 mg LEDD (which is equivalent to 5 mg of rotigotine, 1.5 mg of pramipexol and 7.5 mg of ropirinol), sustained a strong association with DAWS development. (Table 3, *p* = 0.018; OR = 5.3; 95 % CI 1.5–21). There was not significant differences among the dopamine agonist. Duration of PD in years, total dopaminergic burden, UPDRS Ib and II, GAD 7 and PHQ9, did not show significant difference (Table 2).

With reference to adverse effects to dopamine agonist, the presence of ICD displayed a significant association with DAWS (*p* = 0.002; OR = 5.2; 95 % CI 1.8–16). Idiosyncratic and general adverse effects to dopamine agonists, speed of taper, total versus partial withdrawal and presence or absence of other antiparkinsonian medications, did not show association with DAWS (Table 3).

History of DBS surgery prior to the withdrawal of dopamine agonist, was associated with DAWS development (Table 3, *p* = 0.049; OR = 12.9; 95 % CI 2–94). Five patients had DBS in STN and the remaining one in GPi. The three subjects who developed DAWS were stimulated in the STN.

A bivariate logistic regression (DAWS vs NO DAWS) was performed with the identified associated factors: presence of a dopamine agonist dose  $\geq 150$  mg LEDD, ICD and prior DBS surgery. The coexistence of the 3 factors was associated with 92 % of probability for DAWS. Two factors increased the probability up to 70 %, whereas one factor up to 30 %. The absence of the three factors was associated with a probability of DAWS development of 3 %. The goodness of fit of this model was 84 %.

**Table 2**  
Demographic, clinical and treatment variables (quantitative) at the time of the withdrawal among NO DAWs and DAWs patients.

Columnal	NO DAWs (n = 104)	DAWs (n = 21)	p
Age mean (SD)	65.1 (9.1)	64.1(10.3)	0.98
Gender males n (%)	54 (51.9 %)	11 (52.4 %)	0.96
Marital Status n (%)			0.89
Single	8 (7.7 %)	10 (9.5 %)	
Married	77 (74.0 %)	17 (81.0 %)	
Divorced	8(7.7 %)	1 (4.8 %)	
Widowed	9 (8.7 %)	1 (4.8 %)	
Unknown	2 (1.9 %)	0 (0 %)	
Race n (%)		0.63	
Caucasian	96 (92.3 %)	21 (100 %)	
African American	1 (1 %)	0 (0 %)	
Asian	2 (1.9 %)	0 (0 %)	
Other	5 (4.8 %)	0 (0 %)	
Smoking history n (%)		0.22	
Never	62 (59.6 %)	10 (47.6 %)	
Former light smoker	8 (7.7 %)	2 (9.5 %)	
Former heavy smoker	23 (22.1 %)	9 (42.9 %)	
Current light smoker	0 (0 %)	0 (0 %)	
Current heavy smoker	3 (2.9 %)	0 (0 %)	
Quit unknown quantity	8 (7.7 %)	0 (0 %)	
PD duration years (SD)	83 (6.4)	3.8 (4.5)	0.38
Dopamine agonist duration (months)	28.6 (33.0)	29.5 (20.6)	0.26
Total dopaminergic burden (LEDD)	723.7 (506.7)	592.8 (178.6)	0.21
Daily dose of dopamine agonist (LEDD)	174.9 (126.7)	235.7 (133.5)	*0.006
UPDRS Ib	7.3 (4.9)	6 (2.6)	0.6
UPDRS II	15 (9.5)	8.8 (5.3)	0.42
Anxiety (GAD 7)	4.8 (5.5)	4.4 (4.1)	0.14
Depression (PHQ9)	7.0 (5.3)	3.8 (3.7)	0.71

**Table 3**  
Treatment variables (categorical) among NO DAWs and DAWs patients at the time of the withdrawal.

	n	NO DAWs (n = 104)	DAWs (n = 21)	p
Medications at withdrawal				
Only DAgo	18	16 (88.9 %)	2 (11.1 %)	0.48
DAgo dose Lmeq >150	72	55 (76.4)	17 (23.6)	*0.018
Taper amount				
Complete	104	87 (83.7 %)	17 (16.3 %)	0.76
Speed of taper <2 weeks	106	88 (83.0 %)	18 (17.0 %)	0.97
Adverse effects				
ICD	23	9 (39.1 %)	14 (60.9 %)	*0.002
Idiosyncratic	25	6 (24.0 %)	19 (76.0 %)	0.28
General	63	9 (14.3 %)	54 (85.7 %)	0.44
DBS				
Previous DBS	6	3 (50 %)	3 (50 %)	*0.049

**Table 4**  
Summary of main findings across previous DAWs studies.

Main author study	Number of patients	DAWs	NO DAWs	% DAWs development	mean LEDD of dopamine agonist	High dopamine agonist dose as associated factor for DAWs	ICD as associated factor for DAWs	DBS as associated factor for DAWs
Rabinak (10)	26	5	21	23.8	420	YES	YES	variable not included
Cunnington (13)	46	7	39	17.9	440	NO	YES	variable not included
Pondal (11)	84	13	71	18.3	239	NO	YES	variable not included
Limotai (12)	358	26	332	7.8	336	NO	YES	NO
Current study	125	21	104	20.2	235	YES	YES	YES

## 5. Discussion

DAWs has become a recognized condition that carries serious impact in patients and caregivers. With no standard treatment available prevention constitutes the main strategy, hence identification of associated factors can lead to improve clinical decision making.

Previous studies have shown a frequency of the syndrome from 8 % to 24 % [10,13,16]. Using the Rabinak and Nirenberg criteria [10] our chart review demonstrated a similar frequency (20.1 %). None of the demographic characteristics was associated with an increased risk of DAWs in the present or past studies (Table 4).

A high rate of missing data prevented us from analyzing highest level of education, job status and history of abuse of substances. In relation to medication dosage, previous studies have shown association of higher doses of dopamine agonists with higher risk of DAWs [10,13]. In our case the same trend was evidenced, with a dose  $\geq 150$  LEDD of dopamine agonist per day being a significant associated factor (OR = 5.3). Formerly, DAWs has been suggested to occur exclusively in patients with ICD [10]. In our study, 9 out of 21 patients with DAWs (42.8 %) experienced this kind of adverse reaction, showing that this condition can take place in absence of ICD, finding that has been observed by Pondal and Limotai cohorts [11,12]. Interestingly, the presence of ICD increased the risk of DAWs in our population (OR = 5.2). This implies that presence of ICD is a risk factor, but not a *sine qua non* condition for DAWs occurrence. A previous publication has linked DAWs development to lower UPDRS motor scores. However, is important to highlight that these results (Rabinak and Nirenberg) display a statistically significant difference between dopamine agonist LEDD in the group of DAWs vs NO DAWs (p = 0.04) [10]. Patients who developed DAWs received almost the double dose of dopamine agonist therapy expressed in LEDD (420 vs 240 compared to NO DAWs group). The lower UPDRS scores in the DAWs group can be a consequence of the Dopamine Agonist dose and not necessarily and independent associated or risk factor for DAWs development. In the present study, motor UPDRS score was not included as an analysis variable. However, UPDRS parts IB and II showed a tendency to be lower than NO DAWs group, but no statically significant difference was present. None of the prior studies have included analysis of UPDRS I or II. Of note, our population had a lower dose of dopamine agonist compared with most populations in previous analysis [11,13], fact that can explained by the differences in terms of clinical decision, guides and protocols over institutions and regions.

Some symptoms related to DBS procedure can be similar to DAWs symptoms. Therefore, the relation between these factors has been difficult to analyze and remains controversial. Only one study included patients with the antecedent of the procedure, but no statistically significant association with DAWs was established [12]. Nevertheless, 14 patients with DBS developed the syndrome, 11 of them after the procedure, 3 in the preoperative phase. Twelve out of 14 had STN implant. In our case 3 out of 6 patients (50 %) with history of DBS developed DAWs. We emphasize that all these patients had the insertion of the device, at least 12 months before withdrawal of dopamine agonist, and STN was the target in the 3 cases. The small sample is a limitation in the interpretation, but these findings point towards the consideration of DBS

as an associated factor of DAWS development specially when STN is the anatomic target. Some reports suggest that mesolimbic STN denervation may facilitate impulsivity in the post operative scenario [17], fact that could be related to DAWS development in this particular setting.

Our study has limitations linked to the retrospective chart review design. Missing information prevented us from including other variables of interest, and conclusions need to be interpreted with caution given the small sample size.

In summary, DAWS is a defined condition entailing a significant impact. Different retrospective studies have identified association of the syndrome with presence of ICD, high doses of dopamine agonist, duration of dopamine agonist treatment, and total dose of antiparkinsonian treatment at time of withdrawal. Our study suggests that dose of dopamine agonist  $\geq 150$  LEDD, presence of ICD and prior history of DBS, are significant associated factors for DAWS development. Prospective designs with larger samples are needed to confirm these findings.

#### CRedit authorship contribution statement

**Xiomara Garcia:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Mohammad Edrees Mohammad:** Data curation, Writing – review & editing. **Shnehal Patel:** Data curation, Writing – review & editing. **Xin Xin Yu:** Data curation, Writing – review & editing. **Hubert H. Fernandez:** Supervision, Project administration, Writing – review & editing.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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