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CLINICAL PRACTICE

RESEARCH ARTICLE

A Pilot Prospective, Multicenter Observational Study of Dopamine Agonist Withdrawal Syndrome in Parkinson's Disease

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Abstract: Dopamine agonist withdrawal syndrome (DAWS) has been reported in patients with Parkinson's disease (PD) who rapidly decrease or stop their dopamine agonist (DA) treatment. Retrospective studies suggest a high prevalence of DAWS (14%–18%) in PD, but there are no prospective studies. We report data from the first pilot European multicenter prospective study addressing the frequency of probable DAWS (Rabinak-Nirenberg criteria) in PD patients. The self-completed Nonmotor Symptoms Questionnaire (which addresses the core features of DAWS) was administered at clinical follow-up at 1 month in 51 patients (33 male; mean age: 73.0 ± 9.9 years; PD duration: 12.2 ± 6.3 years) who had discontinued dopamine agonists. Twelve out of fifty-one patients (24%) met clinical criteria for DAWS, the most common symptoms of which were anxiety (91.7%), pain (50%), sweating (41.7%), and anhedonia (16.7%), after the withdrawal of a DA (ropinirole, pramipexole, or cabergoline). In this first prospective evaluation of DAWS in the clinic, preliminary data indicate a high rate after discontinuation of a range of DAs, particularly in the context of impulse control disorders. Larger, controlled studies are required to establish a definitive management pathway.

Dopamine agonist withdrawal syndrome (DAWS) has emerged as a therapeutic challenge in Parkinson's disease (PD). The reported symptoms are stereotyped and consist of psychiatric, autonomic, and sensory symptoms, similar to those of addictive drug withdrawal.[1] The condition has been recently characterized and described in people with PD who decrease or stop their dopamine agonist (DA) treatment.[2,3] A prevalence of DAWS of 14% to 18% in PD patients who taper a DA has been reported in retrospective studies, with an even higher prevalence in those who taper a DA in the setting of baseline impulse control disorders.[1,2] At this time, we are not aware of any prospective studies addressing the frequency of this problem in the clinic.

We report a prospective, multicenter, observational study that specifically addressed occurrence of DAWS in consecutive PD patients on DA treatment who underwent stoppage of DA treatment using the DAWS criteria defined by Rabinak and Nirenberg, supplemented by relevant questions on the Nonmotor Symptoms Questionnaire (NMSQuest).[4]

Patients and Methods

For a period of 6 months (November 2012–May 2013), all PD patients whose DA treatment was tapered and stopped were specifically monitored for development of DAWS by investigators in 10 centers across Europe. The criteria used for development of DAWS were pragmatic and were based on the expert advice and guidelines reported by Rabinak[1] and utilized the use of the NMSQuest, a validated self-reported nonmotor symptoms (NMS) tool addressing 30 NMS.[4] NMSQuest contains questions in a "yes" and "no" format that are described as typical symptoms of DAWS. In addition, in all suspected DAWS

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cases, a clinical interview seeking corroboration was performed as part of routine clinical follow-up. All PD patients were specifically informed about DAWS and asked to complete an NMSQuest at approximately 1 month after DA was stopped when reviewed in clinic. All patients had NMSQuest performed before any stoppage of DA as part of routine clinical practice allowing a pre- and postcomparison of self-declared NMS. If the patient developed clinical features of DAWS (as per Rabinak and Nirenberg guidelines), we classified their symptoms as mild, moderate, or severe, based on clinical severity as per clinical judgment of the investigators. If the patients had a large number of related NMS as per NMSQuest and rated the symptoms as severe and intrusive, then they were considered to have severe DAWS. The need for reintroduction of DAs or supplementation of levodopa to compensate the effect of stopping DAs was also noted.

The study was an observational audit of clinical practice (CASS code no. 2913) in an outpatient clinic and was also part of a 5-year NMS natural history study (NILS) of PD, which was approved by the ethics committee of relevant institutions and centrally at Kings College Hospital, London (NILS UKCRN no. 10084).

Results

During the observational period, 51 patients were identified who underwent tapering and discontinuation of a DA (ropinirole, pramipexole, or cabergoline) because of side effects, mainly impulse control disorders (ICDs) and hallucinations. Demographic characteristics of the patients (with and without DAWS) are presented in Table 1.

Twelve out of fifty-one patients (24%) were considered to have developed DAWS, according to fulfilling Rabinak-Nirenberg criteria. Taken from the 30-item NMSQuest, the most common symptoms of DAWS were anxiety, pain, anhedonia, and hyperhidrosis (Table 2).

In all 12 cases of DAWS, a baseline (pre-DAWS) assessment of NMSQuest, performed as part of routine clinical care, was available and Table 2 outlines the percentage of individual NMS recorded by patients during presumed DAWS, not present at baseline.

In 4 subjects (33%), symptoms were severe, consisting of pronounced apathy, anxiety, fatigue, and nonspecific malaise. All had discontinued DA and required reintroduction of a small dose of DA to alleviate the symptoms. Moderate and mild cases were also equally distributed. When specifically questioned, none of the patients had been warned about development of DAWS when DAs were started.

Discussion

Our study represents the first prospective observational study addressing the occurrence of DAWS in the clinic, using a multicenter approach. Although this study is preliminary and may include a degree of selection bias in the recruitment of patients, we would still like to highlight the following key points:

1. In patients who reduce or discontinue DA therapy, particularly those with ICDs, DAWS represents a clinically relevant problem. The Rabinak and Nirenberg criteria can be easily applied, and in this study, the DAWS rate is high (at 24%).
2. The symptoms are diverse and largely nonmotor in nature, with anxiety, apathy, fatigue, and pain being the most common and intrusive to lifestyle of patient and carer.
3. Clinically, DAWS can present in mild, moderate, and severe forms. Moderate-to-severe DAWS required low-dose reintroduction of DA.
4. DAWS can also be observed in patients where DA is discontinued because of side effects other than ICDs, such as hallucinations.

We believe this study highlights the growing concern about DAWS, first signposted by Rabinak and Nirenberg, as a clinical challenge.[1] We report a 24% DAWS rate in an unselected consecutive PD population from 10 outpatient clinics secondary to tapering and stoppage of DAs. This figure is similar to that quoted in recent reports (7.8%–19%) and may reflect the prospective design of the study as well as greater information sharing regarding DAWS among clinical personnel as well as patients.[1,2]

TABLE 1 Demographic characteristics of patients with and without DAWS

	DAWS Patients		Non-DAWS Patients	
N	12		39	
Mean age, years	71.5 ± 11.0		73.2 ± 8.7	
Gender (males), %	66.7		56.0	
PD duration, years	11.3 ± 6.3		10.0 ± 7.0	
DA (mean dose: mg)				
Ropinirole	N = 7 (16)		N = 25 (16)	
Pramipexole	N = 4 (2.75)		N = 7 (2.25)	
Cabergoline	N = 1 (1)		N = 0	
Apomorphine	N = 0		N = 7 (100)	
Duration of levodopa and DA treatment, years	7.5		6.3	
	Pre	Post	Pre	Post
DA LED (mg)	272	74	400	192
LED total (mg)	705	802	740	868

LED, levodopa equivalent dose, DA - dopamine agonist

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TABLE 2 Self-declared NMS of DAWS (as noted by NMSQuest) in patients with presumed DAWS (n = 12) and those without (n = 39)

Symptoms of DAWS	Rate (%)	
	DAWS Patients (N = 12/51)	Non-DAWS Patients (N = 39/51)
Anxiety	11 (91.7)	12 (30.7)
Pain (central)	6 (50)	15 (38.4)
Hyperhidrosis	5 (41.7)	3 (7.7)
Anhedonia	2 (16.7)	1 (2.5)
Apathy	1 (8.3)	3 (7.7)
Limb paraesthesia	1 (8.3)	1 (2.5)
Depression	1 (8.3)	0

The symptoms of DAWS are mostly nonmotor in nature and have been recently classified in three main subgroups—psychiatric, autonomic (gastrointestinal), and sensory—and our cases illustrated a medley of these symptoms (Table 2). However, anxiety and pain reminiscent of central pain, and hyperhidrosis associated with anxiety, dominated our cohort with DAWS whereas apathy, depression, and nonspecific paraesthesias were reported in many cases. Anxiety, apathy, and pain led to severe problems with interpersonal relationships in some cases and also a poor quality of life with increased caregiver stress. We have to stress, however, that pain, as assessed in this study, was as described in NMSQuest and the possibility of recurrence of OFF-related dystonia and associated pain cannot be discounted in these cases. This may also account for the fact that pain was relatively common in both DAWS (50%) as well as the non-DAWS group (38.4%).

The clinical literature thus far suggests a high rate of DAWS in patients with clinically relevant ICDs (almost all DAWS cases reported have ICDs).[5] In our series, however, the baseline rate of ICDs causing withdrawal of DA was lower at 33% and DAWS was also evident in patients where DAs had been discontinued because of other DA related side effects, mainly intrusive hallucinations and ankle swelling. In some cases, however, hallucinations had coexisted with ICDs. This anomaly could be owing to a possible underdiagnosis of DAWS in our cohort or the fact that some patients continued with DAs given that ICD was not considered to be significant according to the judgment of the clinician.

In the DAWS patients, we were able to compare and contrast relevant NMS at a stable state preceding DAWS, NMSQuest data being collected as part of standard clinical care and NMS declared during DAWS. Anxiety, pain, apathy, hyperhidrosis, and depression were evident in a large proportion of cases. In these cases, the relevant NMS were not reported at baseline. We can therefore assume that these symptoms arose as part of the DAWS symptomatology. However, in the rest of the cases, these NMS were also present at baseline, and because the NMSQuest is unable to grade rate severity of symptoms, we cannot comment as to whether these symptoms worsened during DAWS. A relatively new aspect of this work is the use of NMSQuest for identification of the NMS related to DAWS. We used the NMSQuest because it is, to date, the only validated and International Parkinson and Movement Disorder Society (IPMDS)-recommended self-declaration tool for NMS in PD; however, we must emphasize that the NMSQuest is not a grade-rating tool; severity assessment of DAWS was thus driven by clinician judgment coupled with the patient-reported NMS in NMSQuest and numbers of NMS reported.

There are several limitations of this study and, in particular, the accurate ascertainment of symptoms, such as central pain or depression, given that we did not use specific instruments validated for PD. However, this is the first study to provide a "holistic" view of the clinical issue of DAWS. Undetected, in many cases, the symptoms of DAWS could lead to a large number of secondary problems, such as marital conflict, job loss, or suicidal ideation, while depression and anxiety are dominant in all cases.[5,6] We also were able to capture the DAWS symptoms by using NMSQuest, which could be used complimentary to the Rabinak and Nirenberg criteria and is widely used for self-declaration of NMS in the clinic and recommended by the IPMDS and the National Institute of Neurological Disorders and Stroke.[7] Clinically, one also needs to be astute given that these NMS could also occur as part of nonmotor fluctuations and thus need careful evaluation.[8] Other limitations include the lack of longer-term follow-up of patients after DA withdrawal and lack of data related to the outcome of DAWS patients, and the latter issue will be addressed by longitudinal data gathered from patients diagnosed as DAWS.

We attempted a pragmatic clinician-driven separation of DAWS in three severity criteria of mild, moderate, and severe. Moderate-to-severe DAWS required low-dose reintroduction of DA. Table 1 shows the dose reductions in DA doses in both DAWS and non-DAWS groups and suggests that the DA dose was decreased, with 73% in the DAWS group versus 52% in the non-DAWS group. This may have clinical relevance, given that our moderate and severe cases needed reintroduction of the discontinued DAs at a lower dose with either complete or partial reversal of DAWS symptoms. This strategy can, however, cause re-emergence of ICDs; close monitoring of patients is therefore essential. This issue also highlights the potential problems for the management of DAWS in the clinic, which, at this time, is unclear and not defined. Recent studies have also focused on identification of potential risk factors for the development of DAWS, and this needs to be clinically adopted similar to the way one would screen for risk factors for development of ICDs.[9] In our experience, all patients diagnosed with moderate-to-severe DAWS needed counseling, intervention with a psychologist, and reintroduction of the previously discontinued DA, particularly given that virtually all such patients may have a degree of ICD.

In the patient population studied, the key DAs implicated were ropinirole, pramipexole, and cabergoline, the latter being used in 1 patient with active monitoring for cardiac valvulopathy. Both short- and long-acting formulations of ropinirole and pramipexole were involved, and cabergoline is a long-acting DA. Hence, in this small study, we could not speculate as to whether DAWS is more common with discontinuation of short- versus long-acting DAs. Interestingly, however, we note that DAWS was not observed in patients on apomorphine infusion (12–16 h/day; Table 1) and the cause of this is unclear,

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and we are unable to make any specific statement because the numbers were too low. However, this observation may form the basis of a prospective study addressing rates of DAWS in patients being treated with a continuous drug-delivery strategy.

These results, however, have to be confirmed and quantitated in larger, controlled studies, given that this was a preliminary, observational, and descriptive one. As such, we are unable to provide any relevant statistical analysis between the groups with and without DAWS. The nature of the study also may explain the higher rate of DAWS reported in this study, owing to the fact that all clinicians taking part in it were aware of DAWS, and currently, all studies published reporting DAWS are retrospective. We also did not assess patients with NMSQuest immediately preceding discontinuation of DA, because this was an observational pragmatic study of clinical practice and not an a priori "before and after" design. As such, we are unable to comment on whether the pre-existing NMS profile of patients influenced the emergence of some NMS in the DAWS patients. Similarly, we are unable to comment on any specific motor worsening during DAWS, although clinical experience would suggest this to be the case with discontinuation of dopaminergic therapy.

The strengths, however, are a prospective design, use of specific criteria for DAWS and supplementation with the NMSQuest, and performing the observations in clinically aware centers. Furthermore, the point that moderate and severe DAWS may need DA supplementation may also be useful for clinicians to note.

In conclusion, we confirm that DAWS is a clinically significant issue in PD patients undergoing DA therapy. High awareness is required in relation to DAWS among clinicians and PD nurses, and the Rabinak and Nirenberg criteria can be easily utilized and supported by use of the NMSQuest. We propose that all patients should be warned about the risk of DAWS before commencement of DA therapy, and that further research should focus on the identification of high-risk patients and treatments for this clinical problem.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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References

1. Rabinak CA, Nirenberg MJ. Dopamine agonist withdrawal syndrome in Parkinson disease. *Arch Neurol* 2010;67:58–63.
2. Pondal M, Marras C, Miyasaki J, et al. Clinical features of dopamine agonist withdrawal syndrome in a movement disorders clinic. *J Neurol Neurosurg Psychiatry* 2013;84:130–135.
3. Sadock BJ, Kaplan HI, Sadock VA. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry*. 10th ed. Philadelphia: Wolter Kluwer/Lippincott Williams & Wilkins; 2007.
4. Chaudhuri KR, Martinez-Martin P, Schapira AHV, et al. An international multicentre pilot study of the first comprehensive self-completed non motor symptoms questionnaire for Parkinson's disease: the NMSQuest study. *Mov Disord* 2006;21:916–923.
5. Nirenberg MJ. Dopamine agonist withdrawal syndrome: implications for patient care. *Drugs Aging* 2013;30:587–592.
6. Limotai N, Oyama G, Go C, et al. Addiction-like manifestations and Parkinson's disease: a large single center 9-year experience. *Int J Neurosci* 2012;122:145–153.
7. Martinez-Martin P, Schapira AH, Stocchi F, et al. Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. *Mov Disord* 2007;22:1623–1629.
8. Storch A, Schneider CB, Wolz M, et al. Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. *Neurology* 2013;80:800–809.
9. Cunnington AL, White L, Hood K. Identification of possible risk factors for the development of dopamine agonist withdrawal syndrome in Parkinson's disease. *Parkinsonism Relat Disord* 2012;18:1051–1052.

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