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Dopamine agonist withdrawal syndrome (DAWS) in a tertiary Parkinson disease treatment center

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ABSTRACT

Introduction: Dopamine agonists are a mainstay of treatment for patients with Parkinson disease (PD). However, side effects limit their use, often necessitating dose change. Upon withdrawal, patients may experience dopamine agonist withdrawal syndrome (DAWS). To date, there is no established protocol for the prevention or treatment of DAWS.

Methods: We performed a retrospective chart review of PD patients who were taking a dopamine agonist.

Results: In our large cohort of 313 PD patients who were on a dopamine agonist, we found that 39.5% (n = 124) had a change in their dose of medication for various reasons, including 102 patients who experienced a side effect on a dopamine agonist. Twenty out of 102 patients (19.6%) developed symptoms consistent with DAWS, whereas 1 out of 22 patients (4.5%) who had medication dose changed due to any other reason (e.g. dyskinesias, DBS surgery, decreased by another provider, etc.) developed symptoms consistent with DAWS. Our DAWS population had a shorter duration of PD, less exposure to a dopamine agonist, and was on a lower dose compared to those patients who did not develop DAWS. Agitation was the most common DAWS symptom reported in our cohort. Interestingly, in terms of developing DAWS, the prevalence of DAWS (19.0% vs 16.5%; p = 0.76) between partial versus total discontinuation was not significantly different whether the dopamine agonist dose was decreased (21 patients) or completely stopped (103 patients).

Conclusion: Contrary to previous reports, we have found that other side effects besides impulse control behavioral disorders also increase risk for developing DAWS. Furthermore, the prevalence of DAWS did not differ between partial versus total discontinuation of the dopamine agonist.

1. Introduction

Parkinson disease (PD) is a chronic neurodegenerative condition affecting 7–10 million people in the world. Without a current cure, the mainstay of symptomatic treatment remains dopamine replacement, including dopamine agonists.

Although consistently providing meaningful benefit in controlling motor symptoms in PD, patients on dopamine agonists can experience significant side effects which can become intolerable. These side effects include cognitive changes, delusions and hallucinations, excessive daytime sleepiness, "sleep attacks", leg swelling, weight gain, and impulse control behavioral disorders (ICD), among others.

Present management of side effects requires tapering or withdrawal of the offending dopamine agonist. However, in our clinical practice, this is often easier said than done. PD patients may experience worsening of their motor symptoms and occasionally they have been described to develop signs and symptoms similar to those seen in patients experiencing psychostimulant withdrawal. This recently recognized phenomenon has been termed dopamine agonist withdrawal syndrome (DAWS) [1–3]

DAWS is a stereotyped, often severe, cluster of physical and behavioral symptoms occurring with dopamine agonist withdrawal, including panic attacks, depression, diaphoresis, agitation, fatigue, pain, orthostatic hypotension, and drug craving, that are refractory to levodopa supplementation [1–3]. DAWS has been reported in up to 19% of patients undergoing a dopamine agonist taper, with a range of 15 to 19%. Risk factors for DAWS that have been reported include high cumulative dopamine agonist exposure, high baseline dopamine agonist dose, and prior diagnosis of ICD [1–3]. Unfortunately, DAWS can be very challenging to treat. It is typically not responsive to levodopa supplementation, antidepressants and other behavioral

Abbreviations: PD, Parkinson Disease; DAWS, dopamine agonist withdrawal syndrome; ICD, impulse control behavioral disorders; LEDD, levodopa equivalent daily dose; KP, Knowledge Program; HSM, health status measures; PHQ9, Patient Health Questionairre-9; GAD7, Generalized Anxiety Disorder 7; UPDRSII, Unified Parkinson Disease Rating Scale II.

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treatments have been minimally effective. The only presumed definitive treatment has been to reinitiate the dopamine agonist [1–3]. In some patients DAWS is self-limiting with resolution within weeks, allowing complete withdrawal of the dopamine agonist. In other patients it can run over a protracted course of months, preventing complete withdrawal of the dopamine agonist, which in turn causing significant unwanted consequences such as a state of chronic ICD leading to litigation, obesity, financial losses, and social and occupational consequences [1–5].

Unfortunately, our cumulative experience with DAWS is limited by small sample size and short observation period. We aim to report the naturalistic phenomenology and prevalence of DAWS as captured in the electronic recorders at our tertiary movement disorders center, with over 1500 PD patients treated annually.

2. Methods

We performed a retrospective chart review of patients diagnosed with PD, by a fellowship-trained movement disorders neurologist, who fulfill the United Kingdom Parkinson's Disease Society Brain Bank criteria, over a 2-year period, from January 2011 to December of 2012, at the Center of Neurological Restoration of the Cleveland Clinic, Cleveland, Ohio. Patients who were not taking a dopamine agonist were excluded from further analysis. Data collected included: gender, race, age at the time of dopamine agonist withdrawal, name of the dopamine agonist, and the duration of PD as well as dopamine agonist use. We then carefully reviewed all notes (in-patient visits, electronic and telephone correspondences) to determine if patient had experienced any symptom that can be considered a side effect of dopamine replacement therapy. Side effects were categorized as follows: (1) *ICD*–hypersexuality, pathological gambling, binge eating, compulsive shopping, punding; (2) *Idiosyncratic dopamine agonist side effects*–leg swelling, weight gain, sleep attacks, skin reactions; (3) *General dopamine replacement therapy side effects*–nausea/vomiting, orthostasis, cognitive worsening, psychosis, sedation.

For all patients, we recorded the total number of PD medications, the daily dose of total dopamine replacement therapy, and also dopamine agonist therapy using published levodopa equivalent daily dose (LEDD) conversion ratios [6]. We further analyzed if patients were continued on the dopamine agonists, or if the dose was tapered or completely stopped. The speed of taper (i.e. <2 weeks, 2–4 weeks, and >4 weeks) was also recorded. Finally, we reviewed if any of these patients experienced symptoms consistent with DAWS including: panic attacks, depression, diaphoresis, agitation, fatigue, pain, drug cravings, or orthostatic hypotension [1–2]. We also collected other demographic variables including education level, job status, marital status, smoking and substance abuse history.

We obtained data through EPIC, our electronic medical record system, and our Knowledge Program (KP). KP is a data capture initiative designed to harness routinely collected clinical information to optimize patient care and use of electronic medical record. Patient reported health status measures (HSM) are collected at each patient visit in electronic tablet, patient kiosk, or from patient's home through patients' electronic access (MyChart). These results, along with data from existing clinical systems, are then consolidated into a single data repository, the KP database. The KP database was able to provide further information regarding patient's depression, anxiety, and the activities of daily living measurements using Patient Health Questionairre-9 (PHQ-9), Generalized Anxiety Disorder 7 (GAD7), and the Unified Parkinson Disease Rating Scale II (UPDRSII), respectively. We used values that were closest to the time when the patient was either taken off the dopamine agonist or their last visit for patients who were continued on the dopamine agonist.

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

3. Statistics

Descriptive statistics was used to describe our cohort. Using the SPSS software, Mann-Whitney was used to compare non-normative data such as demographic data between two different populations (e.g. continued dopamine agonist versus dose reduced or discontinued). Mann-Whitney was also used to compare demographic data of patients with DAWS compared to those without DAWS. Chi-square was used when comparing categorical variables in the population groups (e.g. continued versus decreased versus discontinued dopamine agonist). Chi-square was also used to compare incidence of DAWS between populations based on the type of side effect experienced. Significance was defined as $p < 0.05$.

4. Results

Out of 1884 parkinsonian patients who were seen in Cleveland Clinic over the two-year period, 313 met diagnostic criteria for idiopathic PD and were taking a dopamine agonist. Our cohort had a mean: age (at time of analysis) of 65.1 years (SD 9.2); PD duration of 8.45 years (SD 6.23); duration of dopamine agonist use of 58.5 months (SD 170.7); total daily dopamine replacement dose of 770.5 mg LEDD (SD 429.8); and, daily dopamine agonist dosage of 191 mg LEDD (SD 116.8). Types of dopamine agonists used are listed in Table 1.

Our cohort was then classified according to dopamine agonist dose modification (i.e. no change versus dose decrease/discontinuation). The demographical data of these two groups are also illustrated in Table 2. Education level, job status, marital status, smoking and substance abuse history were unable to be obtained in over half of the cohort, therefore these variables were not included. The duration of PD, duration of dopamine agonist use, and mean dose of dopamine agonist were greater in patients who had continued the dopamine agonist compared to those who had decreased or stopped the medication. Patients whose duration of PD or dopamine agonist use was not known were not included in the mean analysis.

4.1. Evaluation of DAWS based on dopamine agonist side effects

One patient was lost to follow up and was not included. Out of the remaining 312 patients, 50% (n = 156) developed at least 1 side effect. Of these patients, 65% (n = 102) had the dopamine agonist either decreased or completely stopped, whereas 35% (n = 54) continued on the same dose. Of those who had dopamine agonist dose decreased or discontinued, 19.6% (n = 20) developed symptoms consistent with DAWS.

Of the patients who did not experience any side effect, there were 14% (n = 22) who had the medication either decreased or completely stopped. The reasons for decrease were varied and included: patient receiving DBS; having dyskinesias; or medication was changed by another provider for unknown reason. Within this group, only 1 patient (4.5%) developed symptoms consistent with DAWS. This patient has his medication stopped during an inpatient admission for an irregular heart rate, which seemed unrelated to the dopamine agonist.

4.2. Side effects and decision to taper

The 156 patients who developed side effects were then classified according to the types of adverse event experienced: 32 experienced ICD;

Table 1
Type of dopamine agonist used.

Dopamine agonists used	N (%)
Pramipexole	33 (21.15%)
Ropinirole	99 (63.46%)
Rotigotine	24 (15.38)%