Impact of behavioral side effects on the management of Parkinson patients treated with dopamine agonists

Mohammad Edrees Mohammad [a,c], Joaquin A. Vizcarra [b], Xiomara Garcia [c], Shnehal Patel [d], Adam Margolius [c,*], Xin Xin Yu [c], Hubert H. Fernandez [c]

[a] Neurology Department, Kasr Al Ainy Hospital, Egypt
[b] Department of Neurology, Emory University, Atlanta, GA, USA
[c] Center for Neurological Restoration, Neurological Institute, Cleveland Clinic, USA
[d] OhioHealth Neurological Physicians, USA

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ABSTRACT

Dopamine agonists are one of the main stay of treatment option for Parkinson disease (PD). Side effects that develop from their use are generally categorized into *behavioral* and *non-behavioral*. Behavioral side effects include: impulse control behavior disorder (ICD), psychosis and cognitive impairment. Non-behavioral side effects include: nausea/vomiting, "sleep attacks", leg swelling, weight gain and orthostasis. The aim of this study is to evaluate the clinicians' response to PD patients who developed behavioral side effects from dopamine agonists, in comparison to those patients who developed only non-behavioral side effects. We performed a retrospective chart review of all patients diagnosed with PD over a two year period. Among 313 patients who were on a dopamine agonist, 156 reported side effects. Sixty-five patients reported behavioral (with or without non-behavioral) side effects, while 91 experienced only non-behavioral side effects. Forty-nine out of the 65 patients (75.3%) who experienced behavioral side effects had their dopamine agonist dose decreased compared to 53 out of 91 patients (58.2%) who experienced only non-behavioral side effects (Chi square = 4.92, p < 0.05). Patients with behavioral side effects were 3 times more likely have their dose decreased (OR = 3.3; 95%CI = 1.442–7.551; P = 0.005). However, neither taper speed nor the occurrence of dopamine agonist withdrawal syndrome (DAWS) differed between the two groups. Amongst PD patients treated with dopamine agonists, the presence of behavioral side effects independently increased the chance of dopamine agonist dose reduction. Prospective studies are needed to confirm these findings.

1. Background:

Dopamine agonists are frequently used as a monotherapy or in combination with levodopa for Parkinson disease (PD) [1]. Some of the most commonly used non-ergot dopamine agonists are pramipexole, ropinirole and rotigotine, which mainly act as selective D2/D3 receptor agonists [2]. However, they also have high frequency of causing a number of side effects, which can be categorized into *behavioral* and *non-behavioral*. Behavioral side effects include: impulse control behavior disorder (ICD) such as compulsive sexual disorder, gambling disorder, binge eating disorder, compulsive buying disorder, and punding [3]; other behavioral side effects include psychosis and cogni-

tive impairment [4]. Non-behavioral side effects include nausea/vomiting, sleep attacks, leg swelling, weight gain and orthostasis [5].

The mechanism explaining behavioral side effects is not completely understood. One hypothesis postulates that the stimulation of non-motor striatal areas, which are comparatively less denervated than the motor areas in PD, results in dopaminergic dysfunction behaviors [6]. The ideal management for these side effects is the discontinuation of the offending medication with the aim of reversing the symptoms [7]. However, this may be easier said than done in clinical settings. The aim of this study is to evaluate the clinicians' response to PD patients who developed behavioral side effects from dopamine agonists.

* Corresponding author.
  E-mail addresses: Margola@ccf.org (A. Margolius), yux@ccf.org (X.X. Yu), fernanh@ccf.org (H.H. Fernandez).

2. Methods

We conducted a retrospective chart review of all patients diagnosed with PD by a movement disorders neurologist following the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDS-BB) clinical diagnosis criteria for a two year period at the Center of Neurological Restoration of Cleveland Clinic. Only patients who were taking dopamine agonists and developed side effects were included in the study. Then, by manually reviewing each chart, we categorized our patients according to the development of side effects into two groups. The first group includes patients who developed behavioral side effects (i.e. 1. impulse control behavior disorder (ICD), which include but not limited to: compulsive sexual disorder, binge eating disorder, gambling disorder, and punding; 2. hallucinations, 3. psychosis, and 4. cognitive impairment), whether or not they also developed non-behavioral side effects. The second group includes patients who only developed non-behavioral side effects. We further reviewed their charts to assess three outcome variables: decision to taper, speed of taper and development of dopamine agonist withdrawal syndrome (DAWS). Speed of taper was analyzed as a dichotomous variable with a cutoff point of more than 4 weeks versus less than or equal to 4 weeks. Finally, the occurrence of DAWS was defined by the development of at least one of the following symptoms: panic attacks, depression, diaphoresis, agitation, fatigue, pain, drug cravings, or orthostatic hypotension; sever enough to cause social or occupational impairment [8,9].

For all patients, we recorded the age, gender, PD duration, number of side effects, dopaminergic burden in daily levodopa equivalent dose (LEDD) [10], number of other PD medications excluding dopamine agonists, history of deep brain stimulation surgery and performance on Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) functional subscale (Part II), depression and anxiety scales were obtained.

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 give us 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 MDS-UPDRS Part II, respectively. We used values that were closest to the time 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 the Cleveland Clinic Institutional Review Board.

Statistical analyses were conducted using SPSS software V.23. Significance was set at *p = 0.05*. All variables were tested for normality distribution. Normally distributed variables were compared using an independent sample *t*-test. Dichotomous and ordinal/interval/ratio variables were compared using Chi-square and Mann-Whitney *U* test, respectively. A bivariate logistic regression analysis was conducted to determine the association between the decision of tapering the dopamine agonist and the presence of a behavioral side effect, adjusting for possible confounders: age, gender, duration of PD, dopamine agonist dose, number of side effects, number of PD medications aside from dopamine agonist, MDS-UPDRS Part II, ropinirole and rotigotine use, and the presence of anxiety defined as above. Non-statistically significant adjustors and those observed to not increase the quality of the model were removed from the regression analysis. A final logistic regression was conducted with the remaining variables, collecting their individual odds ratio.

3. Results

Out of 313 PD patients who were on dopamine agonist therapy, 156 patients with a mean: age of 64.08 ($\pm$9.81) years and disease duration of 7.79 ($\pm$6.41) years, developed side effects and were included in the analysis. Out of these 156 patients, 65 (42%) presented with behavioral side effects (with or without non-behavioral) and 91 (58%) developed only non-behavioral side effects. LEDD was calculated using the protocol proposed by Tomlinson et al. [10]. There was a statistically significant difference in demographic features between these two groups in regard to PD duration; LEDD dose; number of side effect; number of other PD medications (besides dopamine agonists); UPDRS Part II score; anxiety; type of dopamine agonists, levodopa and entacapone used (see Table 1). Patients who experienced behavioral side effects had longer PD duration, higher LEDD, increased number of side effects, increased number of other PD medications (besides dopamine agonists), worse functional impairment and higher anxiety symptoms. Of the 65 patients with behavioral side effects, 13 also had non-behavioral side effects. In this group, orthostatic hypotension was the most common non-behavioral side effect (7/13 patients) followed by leg swelling and sleep attacks (3/13 patients each). Of the patients with behavioral side effects, approximately 50% of them experienced some form of ICD. Sedation was the most frequent side effect overall, occurring in approximately 1/3 of patients experiencing any type of side effect (data not shown).

Regarding the decision to taper, 49 out of the 65 patients (75.3%) who experienced behavioral side effects had their dopamine agonist dose decreased compared to 53 out of 91patients (58.2%) who experienced only non-behavioral side effects (Chi square = 4.92, p < 0.05) (See Table 2). Adjusting for covariates including: age, duration of PD, MDS-UPDRS Part II scores, dopamine agonist dose and the presence of behavioral side effects using a decision to taper as a dependent variable, the bivariate logistic regression (r2 = 0.144) of a behavioral side effect had an OR = 3.3 (95% CI 1.442 ~ 7.551, P = 0.005).

Regarding the speed of taper, there was no a statistically significant difference among both groups. 86.2% of our patients were tapered in <4 weeks regardless of the type of side effect. Among our population, 20 patients (12.8%) had developed dopamine agonist withdrawal syndrome (DAWS). The incidence of DAWS does not show a statistically significant difference among both groups.

4. Discussion

While studies that describe a relation between dopamine agonists tapering speed and worsening of PD motor symptoms and incidence of DAWS have been reported [11], to the best of our knowledge, this is the first study exploring the physicians' decision to taper based on the presence of a behavioral side effect. In the current study, we found that PD patients with behavioral side effects were three times more likely to have dose reduction of their dopamine agonist than those who didn't present with behavioral side effects. Even after adjusting for possible confounders, the presence of a behavioral side effect was the largest risk factor for the tapering decision. Our results are similar to some reports describing ICD as the most common cause for tapering decision [8]. This is most likely due to the disruptive nature of these side effects and their interference with daily activities. Ideally, dopamine agonist side effects are managed by tapering the medication. However, despite the potential social impacts of behavioral side effects, in our study we found that dopamine agonist dose was not adjusted in 24.6% of our patients. This could be attributed to the mildness of side effects, the high risk of motor worsening, physician experience and bias.

Of all patients that presented with a dopamine agonist side effect, 86.2% were tapered in <4 weeks regardless of the type of side effect.

Table 1
Baseline characteristics.

		Behavioral S.E + (n = 65)	Non-behavioral S.E (n = 91)	P value
Age		65.32 ± 10.6	63.19 ± 9.2	n.s."
Gender (male: female)		41:24	47:44	n.s.*
PD duration (year)		9.17 ± 7.0	6.80 ± 5.8	P < 0.05^
LEDD dose		866.6 ± 381.7	625.4 ± 387.6	P < 0.01"
Dopamine agonist dose at time of withdrawal		207.4 ± 120.1	188.3 ± 115.4	n.s.^
Number of side effects		1.48 ± 0.99	1.13 ± 0.37	P < 0.05^
Number of other PD med (not dopamine agonists)		1.52 ± 0.89	1.20 ± 0.81	P < 0.05^
UPDRS II (n = 139)		16.1 ± 8.9	11.50 ± 6.82	P < 0.01"
Gad-7 for anxiety > 6 (total n = 133)		13.5 % (n = 18)	11.3% (n = 15)	P < 0.05*
Depression PHQ-9 Categories (n = 150)	None (n = 61)	15.3%	25.3%	n.s.*
	Mild (n = 54)	14.7%	21.3%	
	Moderate (n = 21)	6.7%	8.0%	
	Severe (n = 13)	5.3%	3.3%	
	DBS- (n = 140)	36.5%	53.2%	

DBS = deep brain stimulation.
*P value was obtained using Chi-square.
"P value was obtained using independent sample T-test.
^P value was obtained using Mann-Whitney U test.

Table 2
Outcomes.

		Behavioral S.E	Non-behavioral S.E	P value
Taper decision (n = 156)	Yes (n = 102)	31.4% (n = 49)	34% (n = 53)	P < 0.05*
	No (n = 54)	10.3% (n = 16)	24.4% (n = 38)	
Speed of taper (n = 102)	<4 weeks (n = 88)	38.2% (n = 39)	48% (n = 49)	n.s*
	More than 4 weeks (n = 14)	9.8% (n = 10)	3.9% (n = 4)	
DAWS development (n = 156)	Yes (n = 20)	7.7% (n = 12)	5.1% (n = 8)	n.s*
	No (n = 136)	34.0% (n = 53)	53.2% (n = 83)	

*P value was obtained using Chi-square.

This means that once the tapering decision is made, physicians generally will try to taper it in the shortest period of time.

Interestingly, in our study, the occurrence of DAWS did not differ between these two groups. While this may be in contrast with previous studies that identified ICD as a risk factor for DAWS [8,11], our analysis included other non-ICD behavioral risk factors like psychosis, delusions and cognitive impairment which can dilute the effect of ICD alone as a risk factor for DAWS outcome. Furthermore, our study could lack power to detect small differences in that subgroup.

In general, the decision of whether or not to taper off of dopamine agonist therapy should be individualized according to each patient and should take several factors into consideration including the age of the patient, the stage of PD, the duration of taking the DA, and the concomitant symptoms. However, we have proposed a general guideline to aide clinicians in making this decision (Fig. 1).

There are several limitations in our study. The retrospective design makes our results more applicable to our tertiary care PD population. PD patient severity was inferred through the duration of PD and MDS-UPDRS Part II scores, but no other comprehensive tests, such as psychiatric consultation or neuropsychological testing were used to assess the real magnitude of the disease. Confounders were assessed using a logistic regression analysis, but it is still possible that unknown confounders were not explored.

In conclusion, our study suggests that the presence of a behavioral side effect increases the chance of having dose reduction of dopamine agonist. This reflects how seriously physicians think respond to side effects such as ICD, cognitive impairment and psychosis. Prospective studies are needed to confirm these findings.

Fig. 1. Decision tree for management of patients on dopamine agonists who are experiencing side effects.

CRediT authorship contribution statement

Mohammad Edrees Mohammad: Conceptualization, Methodology, Investigation, Writing - original draft, Formal analysis, Visualization. **Joaquin A. Vizcarra:** Conceptualization, Methodology, Investigation. **Xiomara Garcia:** Conceptualization, Methodology, Investigation. **Shnehal Pate:** Conceptualization, Methodology, Investigation. **Adam Margolius:** Writing - review & editing. **Xin Xin Yu:** Conceptualization, Methodology. **Hubert H. Fernandez:** Conceptualization, Supervision, Methodology, Writing - review & editing.
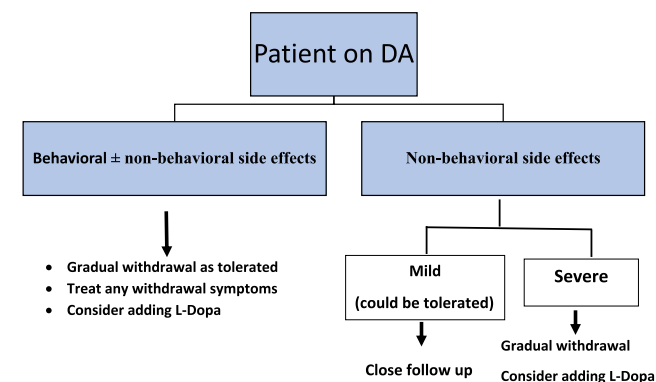
Declaration of Competing Interest

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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