Predictors of Impulsivity and Reward Seeking Behavior With Dopamine Agonists

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ABSTRACT

Objective: To determine risk factors for increased impulsive behavior (gambling, spending, sexuality) in subjects taking dopamine agonists for Parkinson's disease and restless legs syndrome. **Methods:** We interviewed 300 consecutive patients (149 female, 151 male), seen over a ten month period by a single neurologist, taking DA either for PD (207), RLS (89), or both (4). Patients took pramipexole (199), ropinirole (86), pergolide (13), and bromocriptine (1). Specifically, we asked about any changes in gambling, spending, sexual activity, or other impulsive activity subsequent to the initiation of DA. We also queried a series of demographic and medication data. Data was entered into simple and multiple logistic regression models to identify risk factors for impulsivity. **Results:** Overall, 59/300 (19.7%) patients reported any increased impulsivity: 30, any gambling; 26, increased spending; 11, increased sexual activity; and 1, traveling around the country. Overall, only 11/59 (18.6%) with some change felt the change was deleterious. Seven, all PD patients, reported problematic gambling, including two subjects who experienced gambling on pramipexole, but not subsequently on ropinirole. Increased impulsivity correlated with a younger age (O.R.: 0.85 per every additional five years, p=0.01) and larger doses of DA (O.R.: 1.30 per 1 mg of pramipexole or 3 mg of ropinirole, p<0.001). These behaviors were also significantly associated with PD, as opposed to RLS (O.R. 3.27, p<0.01), but lost significance after correcting for dose (O.R.: 2.08, 95% CI (0.88, 4.90), p=0.09). Pramipexole tended to have a higher association than ropinirole (O.R. 1.39), but the relationship was not statistically significant by drug when corrected for dose (p=0.32). **Conclusion:** Increased gambling, spending, and sexuality are commonly associated with DA. This can be problematic but the majority of patients felt that the changes were either neutral or beneficial. Therefore, we feel that "pathologic" impulsivity is part of a spectrum.

INTRODUCTION

Recent attention has focused on pathologic gambling associated with dopaminergic medications when used for Parkinson's disease (PD).[1-12] Other behaviors variably called "dopamine dysregulation syndrome"[13] or "hedonistic homeostatic dysregulation"[14] have also been reported associated with excessive dopaminergic drug use. This is particularly striking because PD patients are generally risk adverse and often have reduced reward seeking behavior at baseline.[15, 16]

Reports have focused on deleterious or "pathologic" behaviors using criteria usually defined or patterned after the DSM-IV.[17] Some risk factors for these pathologic behaviors have been reported.[11,18] However, the prevalence of "pathologic" cases, especially gambling, is usually less than 5%, thus greatly minimizing statistical power to find meaningful cross-sectional associations.

We feel that these "pathological" DA associated behaviors represent a spectrum that begins with, and usually continues to be, mild, and even desirable changes. We have observed general increased reward seeking or immediate gratification (delayed discounting) behavior in this population. Loosely, this equates to impulsivity. Specifically, this included gambling, increased spending and increased sexual activity and desire, including infidelity. We have therefore prospectively evaluated all consecutive patients taking DA for both PD and restless legs syndrome (RLS) to evaluate risk factors associated with any subjective increase in these behaviors in order to better understand their pathogenesis.

TABLE 1:

	PD (n=211)#	RLS (n=89)	Total (n=300)
Sex	Male: 119 (56.4%) Female: 92 (43.6%)	Male: 32 (35.9%) Female: 57 (64.0%)	Male: 151 (50.3%) Female: 149 (49.7%)
Current Age (years)	63.8± 10.4	60.9± 13.5	62.9± 11.9
Age at Onset (years)	54.3± 11.5	38.5± 20.1	49.3± 16.6
Patient status	New: 17 Established: 194	New: 13 Established: 76	New: 40 Established: 260
Drug	Pram: 141 (66.8%) Rop: 57 (27.0%) Perg: 13 (6.2%) Brom: 1 (0.4%)	Pram: 58 (65.2%) Rop: 30 (33.7%) Perg: 1 (1.1%)	Pram: 199 (66.3%) Rop: 87 (29.0%) Perg: 13 (4.7%) Brom: 1 (0.3%)
DA Dose	3.1± 1.3 mg	1.3± 1.2 mg	2.5± 1.9 mg
Duration of DA Use (months)	48.3± 36.4	35.6± 30.6	44.4± 31.8
Concurrent levodopa Dose:	148 (69.6%) Dose: 666.9± 324.9	0	148 Dose: 666.9 324.9
Any Increased Impulsivity	51* (24.6%) 28 gambling 19 shopping 11 sexual 1 driving	8* (8.6%) 2 gambling 7 shopping	59* (19.7%) 30 gambling 26 shopping 11 sexual 1 driving
Serious Gambling	7 (3.4%)	0 (0%)	7 (2.3%)

Includes 4 subjects with both RLS and PD since dosing was for PD
* Some subjects reported more than one type of impulsive behavior
DA = dopamine agonists, Pram = pramipexole, Rop = ropinirole, Perg = pergolide, Brom = bromocriptine

METHODS

The protocol was approved by the Baylor College of Medicine Institutional Review Board. A single neurologist interviewed 300 consecutive patients (149 female, 151 male), seen over a ten month period, taking DA either for PD (207), RLS (89), or both (4). Since RLS symptoms are common in PD, 19 only patients with RLS symptoms beginning more than 10 years before PD onset are included as "both." Each condition was diagnosed using standard criteria. 20 Only patients currently taking DA were included. However, if patients stopped DA specifically because of gambling or other impulsive problems in the past, we included that patient with data from the last date they were taking the DA in order to avoid de-selection bias. Patients that stopped DA for other reasons prior to the study are not included. We only asked about current symptoms in those taking DA to minimize recall bias.

Specifically, we asked about changes in behavior since taking DA. We queried gambling, including online gambling games without actual monetary renumeration; changes in spending behavior thought not to simply result from changes in financial circumstances; and changes in sexual behavior or desire, including infidelity. We also included an open ended miscellaneous category. These four categories were rated on a three point scale. We did not use any published criteria for impulse control problems because we were not trying to identify "pathologic" behavior, but only changes in behavior consistent with increased immediate gratification that was temporally associated with DA use, therefore increasing the sensitivity for finding associations to this unique iatrogenic condition. We also queried a series of demographic and medication data including age, sex, status (new or established visit), age of onset, levodopa dose, and duration of continuous DA therapy.

Data was entered into simple and multiple logistic regression models to identify risk factors for impulsivity.[21] We also separately evaluated the PD and RLS groups. Dopamine agonist dose was computed using the following ratios: pramipexole(1), pergolide(1), ropinirole(0.33), bromocriptine(0.1). Levodopa dose was calculated: (levodopa + levodopa controlled release(0.7))*1.1 if they took catechol-O-methyltransferase inhibitors. The statistical analysis was performed using SAS 9.1, SAS Institute 2005, Cary, NC.

RESULTS

Patient demographics are summarized in Table 1. DA included pramipexole (199), ropinirole (87), pergolide (13) bromocriptine (1). Overall, 59/300 (19.9%) of patients reported any increased impulsive behavior: 30, any gambling; 26, increased spending; 11, increased sexual activity; and 1, traveling around the country. Eleven reported multiple impulsive symptoms. Increased impulsivity in general correlated with a younger age (O.R. 0.85 per every additional five years, p=0.01) and larger doses of DA (O.R. 1.29 per 1 mg of pramipexole or 3 mg of ropinirole, p<0.001). These behaviors were also significantly associated with PD, as opposed to RLS (O.R. 3.27, p<0.01); and marginally associated with a longer duration of disease (P=0.11). The addition of levodopa and levodopa dose, sex, and duration of DA therapy were not associated. Pramipexole tended to have a higher association than ropinirole (O.R. 1.42, 95%CI: (0.72, 2.82)), but the relationship was not statistically significant (p=0.32).

The type of disease was significantly associated with the impulsive systems. PD patients had a higher probability of impulsive systems (O.R. 3.11, 95% CI (1.40, 6.85), p<0.01). However, this strong association became less significant (O.R. 2.08, 95% CI (0.88, 4.90), p=0.09) after correcting for the effect of total DA dose, which was a significant risk factor of impulsive symptoms (O.R. 1.23, 95% (1.05, 1.45), p=0.01) in the multiple logistic regression.

When evaluating only for pure PD (n=207), significant risk factors for impulsivity (n=51, 24.6%) included a younger age of onset (p<0.01), younger current age (p<0.01), and larger DA dose (p=0.02). Pure RLS (n=89) had a lower rate of impulsivity (n=8, 8.6%), which was not predicted by any evaluated factors.

Seven PD subjects (2.3% of total population, 3.4% of PD population) were felt to have pathological gambling, and all lost at least $10,000 U.S. Three of these also reported increased spending and one reported a marked increase in sexual activity. Four were male. Their current age was 59.4 ±7.2, age of onset was 49.4 ±10.7, and DA dose was 3.9 ±2.1 mg/day. At the time of their gambling, six were on pramipexole and one was on pergolide. Two of these patients stopped all DA prior to the survey, and two who experienced gambling while on pramipexole switched to equivalent doses of ropinirole without recurrence.

Two subjects who experiencing marital infidelity, and two subjects with marked increased spending felt that these behaviors were problematic, but all four stayed on DA. Overall, only 11/59 (18.6%) with some change in impulsivity felt that the change was deleterious.

DISCUSSION

We found that increased reward seeking behavior or impulsivity is common in patients taking DA for PD, but less common in those with RLS. In PD, it was associated with younger age and higher DA dose, and marginally associated with a longer duration of disease. Neither sex nor additional levodopa were associated. Pramipexole tended to have higher impulsivity associations but this was not significantly different than ropinirole.

An association with higher dose was reported in one[18], but not another prospective trial looking for pathologic gambling/sexual behaviors.[11] Other retrospective trials have suggested a dose effect.[22] The dose effect is intuitive but may be difficult to interpret. Risk factors for "compulsive (increased) dopaminergic use" include younger age and increased impulsivity.[22] Drug abuse in general is also associated with immediate reward seeking behavior and impulsivity.[23] Therefore, the same physiology that causes the gambling etc., may cause patients to take more dopaminergics, rather than the dopaminergics independently causing the behavior. In turn, causality is difficult to prove.

In contrast to some reports[12], we did not find that additional levodopa contributed to impulsivity. We also found no significant difference between ropinirole and pramipexole. However, all problematic gambling was seen with the more potent D3 agonist (pergolide or pramipexole), and pramipexole tended to be associated with greater impulsivity in general.

Dopaminergic systems are highly implicated in gambling and other reward physiology in general. CSF dopamine metabolites are altered in some studies of gambling.[24,25] MAO-B activity is decreased in gamblers[26-28], and specific dopamine receptor alleles have been associated with pathologic gambling and impulsivity.[29-32] Most importantly, numerous animal and human imaging studies implicate dopaminergic systems in a variety of reward paradigms.[33-36]

Specifically, the ventral tegmental area (A10) dopaminergic system appears central to reward mechanisms, especially variable rate conditioning, or "appetitive" rewards such as gambling.[33,34] These send fibers via the ventral striatum, as well as nucleus accumbens, olfactory tubercle, and Islands of Calleja.[37,38] This has potential clinical relevance since this system contains relatively more D3 receptors than the nigrostriatal "motor" system, which receives dopaminergic input from the ventral tier of the substantia nigra pars compacta, and is earlier affected in PD.[38] In general, dopamine agonists have greater D3 affinity than dopamine. Of the drugs commonly used to treat PD in the United States, the D3/D2 affinity ratio is highest for pramipexole and pergolide, medium for ropinirole, and relatively lowest for dopamine (levodopa). Therefore, the relative higher rates seen in pramipexole, and lack of contribution from levodopa, could have a physiologic rationale.

Reward mechanism physiology has been specifically assessed in PD subjects at baseline using FDG PET in a monetary reward task paradigm.[15,33] Compared to controls, PD patients show markedly less activation in the striatum. All other areas that normally activate (midbrain, thalamus, dorsalateral cortex, and orbitalfrontal cortex) were similar to control subjects. Other impulsive/addictive behaviors also demonstrates increased striatal activity.[39-41]

Like us, other studies have reported that younger age was a risk factor for impulsive behavior[18], however, this was difficult to evaluate because previous studies also included patients not taking DA. Since DA are generally used by younger patients, interpretation of age is greatly confounded unless DA patients are evaluated separately. Increased impulsivity with younger age may not be disease-specific, as age lessens reward seeking behavior in general and greatly reduces the typical pattern of functional imaging in reward seeking paradigms.[33]

DA associated gambling is often referred to as "compulsive." Although semantically equivocal, we disagree with this usage due to its association with obsessive-compulsive disorder or personality disorder. Gambling is classified as an impulse control abnormality[17] and is perpetuated by variable rate positive operant conditioning. Pathological gambling is associated with impulsivity, immediate reward seeking behavior and specific functional imaging findings, which are in marked contrast to those seen in obsessive compulsive disorder.[42-44]

To our knowledge this is the first report to evaluate for DA associated "change" in subjective reward seeking behavior, rather than "pathologic" behavior, is the largest report of DA users, and is the first to evaluate RLS patients. Potential weaknesses of the study include the lack of standardized criteria used to diagnose these conditions. However, since we were looking only for changes from baseline, rather than "pathological" conditions, established criteria would not necessarily apply to this novel iatrogenic condition. Recall bias is an obvious problem in any similarly designed study. We did not query any pre-DA personality characteristics because we did not feel that data would be reliable, given the long duration of continuous treatment in our population (44.4± 31.8 months). We included family input when available but did not systematically separate input of the patients from other family members. Family input at the visit could result in either increased reports of spending. For example the presence of a spouse might increase reports of increased spending or gambling on the part of the patient, or reduce the willingness of the patient to discuss infidelity or gambling with the family there. Subject awareness of "gambling on PD medications" from lay media reports could have altered results. We tried to correct for this by including subjects who stopped DA because of these problems, but could not control for dose modifications made by other physicians. We are a tertiary referral center, but since we were only looking at patients on DA, doubt there was any meaningful difference in our population versus the population in general. No patient was referred to us because of increased reward seeking behavior and no patient declined to participate.

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