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Pathological Gambling in Parkinson's Disease: Risk Factors and Differences from Dopamine Dysregulation. An Analysis of Published Case Series

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Abstract: Pathological gambling (PG) has been reported as a complication of the treatment of Parkinson's disease (PD). We examined all published cases of PG for prevalence and risk factors of this complication, the relationship of PG and use of dopamine agonists (DA), and the relationship of PG to the dopamine dysregulation syndrome (DDS). The prevalence of PG in prospective studies of PD patients using DA has been reported between 2.3 and 8%, compared to approximately 1% in the general population. As in the general population, PD patients with this complication are often young, male and have psychiatric co-morbidity. The vast majority are on DA, often at maximum dose or above. Differences between oral DA failed to reach significance. PG associated with levodopa monotherapy is uncommon, but in the majority of cases levodopa is co-prescribed, suggesting possible cross-sensitization of brain systems mediating reward. PG can occur with DDS but often occurs in isolation. In contrast to DDS, escalation and self regulation of anti-parkinsonian medication are not usually seen. PG in patients with PD using DA is higher than PG reported in the general population, but shares similar characteristics and risk factors. PG is predominantly associated with oral DA. It often occurs in isolation and may not be associated with DDS, which typically occurs on treatment with levodopa or subcutaneous apomorphine. © 2007 Movement Disorder Society

Key words: gambling; Parkinson's disease; impulse control disorder; dopamine disregulation

Pathological gambling (PG) is defined by DSM IV criteria[1] as a persistent and recurrent maladaptive behavior. It is classified as an impulse control disorder (ICD) and often leads to severe financial embarrassment and breakdown of interpersonal relationships. It occasionally occurs in Parkinson's disease (PD) and has been associated with its treatment with dopaminergic drugs. PG together with hypersexuality, other impulse control behaviors, and stereotyped repetitive activities known as punding[2] are recognized components of dopamine dysregulation syndrome (DDS). DDS is characterized by the overuse of additional nonprescribed dopaminergic medication despite an adequate motor response ("on" state) and is frequently complicated by marked dyskinesia and "off" state dysphoria.[3] The central role of dopaminergic drug therapy in these disorders suggests that they share a common neurobiology and that these may be different manifestations of an underlying vulnerability to developing an ICD. Specific differences in relation to use of dopamine agonists (DA) and demographic characteristics of patients with PG compared with those with DDS may provide important insights. We have determined the demographic characteristics and medication profiles of Parkinson's disease patients who pathologically gamble and examined the prevalence of other DDS behaviors in this group. In addition, we assessed how the overall frequency of each DA used in the PG group related to the prescription of each drug, and specifically whether any particular DA is more implicated in this maladaptive behavior.

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PATIENTS AND METHODS

PubMed literature search using term "gambling" and "Parkinson's disease" or "dopamine agonist" or any of

individually named DAs was carried out for the period up to March 2007. Additional relevant case series referenced by these publications were included.[4–6] Sex, age at presentation of PG, age at onset of PD, disease duration, type of DA used, total levodopa equivalent daily dose (LEDD), and presence of co-morbid psychopathology, including DDS behavior, was recorded for each. LEDD was calculated based on theoretical equivalence used in previous reports.[2]

Statistical Analysis

Categorical data were compared using the χ^2 test and continuous numerical data using the unpaired *t* test. Odds ratio (OR) and confidence intervals (CI) were calculated from available data in retrospective database reviews[7] and prospective screening studies,[6,8–11] where overall prescription rates of individual DA in the screened population were known,[12] using STATA® software (StataCorp LP, College Station, TX).

RESULTS

Prevalence of PG in Patients with PD Compared with That in the General Population

Two large North American epidemiological studies using structured interviews based on the DSM-IV criteria show a prevalence of PG in the general population of 0.42% (USA National Survey, N = 43,093)[13] and 1% (Ontario, Canada, N = 1030)[14] respectively. In PD, the prospective screening studies for PG that replicate this strict methodology and adherence to DSM-IV criteria, including use of an experienced psychiatrist to interview patients,[9] revealed higher rates of PG than the general population. In one study, 4.4% of patients on PD medication and 8.0% on DA fulfilled DSM-IV criteria for PG[10] and in another, the lifetime prevalence of PG in PD was 7.2% in patients using a DA.[9]

Patient Characteristics

Twenty-eight case series were identified with a total of 177 patients, dating from July 2000 to March 2007.[4–11,15–34] There was a male preponderance [118 of 156 (75.6%) patients], mean age at diagnosis of PG of 57.3 years (±9.9, range 30–78, N = 80), mean age at onset of Parkinson's disease of 49.5 years (±10.3, range 18–72, N = 80), and a disease duration of 7.8 years (±4.9, range 2–22, N = 80). Other psychopathologies were reported in 45 of 70 (64.3%), with depression in 38 of 91 (41.8%). Absence or presence of previous gambling behavior was reported in 7 series (N = 29). The majority [23 of 31 (74.2%)] did not gamble before diagnosis of PD. Previous substance misuse was reported in 6 series (N = 25). A minority [14 of 38 (36.8%)] had previous substance misuse, predominantly alcohol. Information on premorbid smoking and caffeine use was not given. Previous impulse control disorder (ICD) was reported in one series.[8] 36.4% of patients with active ICD had ICD behavior prior to PD compared with 3.5% of controls.

Medication Use

DAs were used in 174 of 177 (98.3%) of patients, with DA monotherapy in 17 of 130 (13.1%). This included two patients using a combination of two different DA. The three exceptions were a case of PG related to use of selegiline in combination with L-dopa[27] and two cases related to the use of L-dopa monotherapy.[24,28] L-dopa was the most frequently coprescribed agent, [110 of 130 (84.6%)]. Overall, pramipexole was the most commonly prescribed DA [78 of 177 (44.1%)]. Other agents were ropinirole in 42 of 177 (23.7%), pergolide in 32 of 177 (18.1%), bromocriptine in 13 of 177 (7.3%), and cabergoline in 8 of 177 (4.5%). In six series, the number prescribed each individual DA in the screened population group was given; overall, pramipexole was the most commonly used DA (43.6%), followed by ropinirole (28.9%). In five prospective screening studies, the prevalence of PG in patients taking DA ranged from 2.3% to 8.0% (>6% in four series). In one work,[7] pramipexole was significantly more frequently associated with occurrence of PG, compared with ropinirole ($P = 0.01$). However, overall the difference between treatment with individual DA does not reach statistical significance. The pooled OR of PG associated with pramipexole compared with ropinirole is 1.55, CI 0.88–2.73, $P = 0.13$ (heterogeneity χ^2, $P = 0.32$, fixed effects model) (Fig. 1) and the OR comparing total non-ergot and ergot DA is 1.78, CI 0.89–3.54, $P = 0.10$ (heterogeneity χ^2, $P = 0.088$, fixed effects model). The latter calculation very nearly approaches statistical heterogeneity, but if a random effects model is applied the OR is less statistically significant (OR 1.38, CI 0.49–3.93, $P = 0.55$).

The mean latency of onset of PG from DA initiation was 23.0 months (±24.6, range 1–84 months, N = 30) and from L-dopa initiation 86.9 months (±65.1, range 12–216 months, N = 13). Some patients had been on DA therapy for relatively long periods (18 of 30 ≥1 year and 12 of 30 ≥2 years) with their problem of gambling not becoming clinically evident until dopaminergic treatment was increased. In 7 of 9 cases in one work (N = 9)[7] PG started within 1 month of increasing the dose of a DA, which had previously been initiated.

The mean total LEDD was 909.2 (±621.1) mg and the mean DA LEDD was 308.9 (±146.6) mg, equivalent to 4.6 mg of pramipexole salt content (=3.1 mg base) or

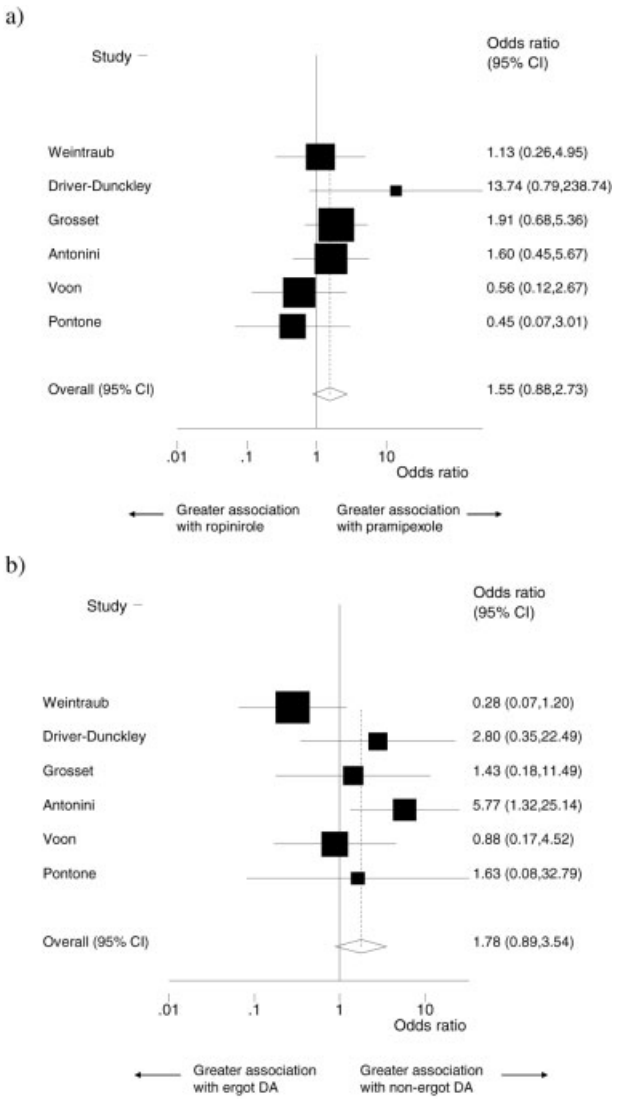

FIG. 1. (a) Odds ratio and 95% confidence interval (CI) for pathological gambling (PG) associated with use of pramipexole compared with use of ropinirole. (b) Odds ratio and 95% CI for PG associated with use of non-ergot dopamine agonists (DA) compared with use of ergot DA.

15.4 mg of ropinirole. The pramipexole equivalent of 4.6 mg (salt) exceeds the maximum recommended dose for this drug. In cases where individual doses of pramipexole were provided (N = 41), 26 of 41 (63.4%) were taking ≥4.5 mg. In cases where individual doses of ropinirole were provided (N = 23), none exceeded the recommended maximum (24 mg), with one patient taking 24 mg. In total for ropinirole and pramipexole (the two most commonly prescribed non-ergot DA), 27 of 64 (42.2%) were taking the maximum recommended dose or more. In works where individual doses of L-dopa were recorded (N = 74), 38 of 74 (51.4%) were using <500 mg, 28 of 74 (37.8%) 500–1000 mg and 8 of 74 (10.8%) >1000 mg, the dose range typical of DDS.

Dopamine Dysregulation Syndrome and Psychiatric Comorbidity

In case series on PG, DDS was explicitly reported in 18 patients, specifically excluded in 53 patients and in the remaining 106 cases, DDS was not specifically reported (Table 1). In those with PG, the DDS and no-DDS groups were similar in terms of their predominantly male sex ($P = 0.62$), early onset of PD ($P = 0.26$), high DA LEDD ($P = 0.42$), and overall history of psychiatric disorders ($P = 0.47$). However, the DDS group had significantly longer disease duration ($P = 0.05$) and higher total LEDD ($P = 0.003$). Directly comparing the non-DDS PG group (N = 50) with a larger (N = 25) representative group of DS,[35] disease duration was significantly longer in patients with DDS ($P < 0.0001$), DA were used less frequently ($P = 0.001$), and L-dopa more frequently ($P = 0.003$). Both DA LEDD ($P < 0.0001$) and total EDD ($P < 0.0001$) were significantly higher in DDS than non-DDS PG (Table 1). The non-ergot DA ($P < 0.0001$) were significantly less associated with DDS behavior than ergot DA. Gambling in the context of an episode of mania is an exclusion criterion in DSM-IV criteria for PG.[1] However, cases of hypomania[9,17] and psychotic symptoms, such as delusional thought disorder,[15] developing after the onset of PG were reported, although this was uncommon.

Type of Gambling

Preferred gambling activities are listed in 17 series (N = 75). These include slot machines in 25/75 (33.3%), casino attendance (activities unspecified) in 16/75 (21.3%), lottery/scratch cards in 12/75 (16%), internet gambling in 15/75 (20%), horse/greyhound racing 10/75 (13.3%), bingo in 4/75 (5.3%), interactive television in 2/75 (2.7%), and stock market in 1/75 (1.3%). This is consistent with previous reports of a predilection for activities which are repetitive, require little higher cortical processing and have high reward uncertainty.

Management

Patient management was detailed in 18 case series (N = 72). Improvement of PG was reported with decrease or discontinuation of DA dose in 29 patients (40.3%), 4 of whom required concomitant increase in L-dopa to control parkinsonian symptoms. Decrease of both L-dopa and DA was required in five patients. In 3 patients L-dopa was decreased with increase of the concomitant DA (cabergoline) in one and with switch from ropinirole to pramipexole in another. Eight others im-

TABLE 1. *Characteristics of patients with pathological gambling (PG) compared with a representative sample of patients with dopamine dysregulation syndrome (DDS)*[a]

	Patients with pathological gambling (PG)				Patients with dopamine dysregulation syndrome (DDS); Evans et al.[35] (Previously unpublished data)	Statistical comparison between patients with DDS and non-DDS PG group
	Total	No DDS	DDS	Statistical comparison of PG patients with and without DDS		
Number (N)	177	50	13	–	25	–
Sex (males)	118/156 (75.6%)	35/50 (70%)	10/13 (76.9%)	NS	19/25 (76.0%)	NS
Age (years)	57.3 (±9.9)	56.2 (±9.3)	61.5 (±7.5)	$P = 0.04$	55.4 (±8.1)	NS
PD onset (years)	49.5 (±10.3)	49.9 (±8.9)	53.0 (±8.1)	NS	42.4 (±8.7)	NS
Duration (years)	7.8 (±4.9)	6.3 (±3.8)	8.5 (±3.4)	$P = 0.05$	13.1 (±5.9)	$P < 0.0001$
All dopamine agonists(DA) (N)	174/177 (98.3%)	50/50 (100%)	12/13 (92.3%)	$P = 0.05$	20/25 (80.0%)	$P = 0.001$
All non-ergot DA (N)	120/177 (67.8%)	42/50 (84%)	5/13 (38.5%)	$P = 0.0008$	1/25 (4%)	$P < 0.0001$
Pramipexole (N)	78/177 (44.1%)	24/50 (48%)	2/13 (15.4%)	$P = 0.03$	0	$P < 0.0001$
Ropinirole (N)	42/177 (23.7%)	18/50 (36%)	3/13 (23.1%)	NS	1/25 (4%)	$P = 0.003$
All ergot DA (N)	53/177 (30.0%)	8/50 (16%)	7/13 (53.8%)	$P = 0.004$	7/25 (28%)	$P = 0.004$
Apomorphine (N)	0	0	0	NS	14/25 (56%)	$P < 0.0001$
Levodopa (N)	110/130 (84.6%)	36/50 (72%)	12/13 (92.3%)	NS	25/25 (100%)	$P = 0.003$
Total levodopa equivalent daily dose (LEDD) (mg)	909.2 (±621.1)	710.4 (±424.2)	1581.7 (±857.5)	$P = 0.003$	1,993 (±833)	$P < 0.0001$
DA LEDD (mg)	308.9 (±146.6)	307.0 (±105.9)	361.2 (±224.9)	NS	706 (±309)	$P < 0.0001$
Ψ history (N)	45/70 (64.3%)	19/33 (57.6%)	9/13 (69.2%)	NS	20/25 (80%)	NS
Depression (N)	38/91 (41.8%)	12/33 (36.4%)	9/13 (69.2%)	$P = 0.04$	12/25 (48%)	NS

[a]Figures given as mean (±SD).

proved after switching to an alternative dopamine agonist (in 6 cases from pramipexole to ropinirole). In patients who responded to dopaminergic dose reduction, 9 needed concomitant psychotherapy and 5 antidepressant prescription. One responded to stopping selegiline. Overall 22 (30.6%) had psychiatric input, of whom 17 had counseling/psychotherapy, 10 were prescribed antidepressants, and 3 an atypical neuroleptic. One patient did not respond to psychotherapy and SSRI, ultimately committing suicide.[7] Ten patients required subthalamic nucleus (STN) stimulation because dopaminergic medication reduction was not tolerated or unsuccessful (N = 9), there was no response to behavioral therapy (N = 4), no response to SSRI (N = 2) or clozapine (N = 1). PG resolved spontaneously in one person. Of the remainder, there was no response to treatment in one (decrease in both L-dopa and pramipexole[25]), no attempted treatment intervention in three[22,28,31] and no information on management in 5 patients.

DISCUSSION

Limitions of Analysis

There are certain major caveats in this type of review that limit generalization of results. These include lack of robust selection criteria and therefore over-reliance on case studies rather than systemic analyses. This is likely to result in selection bias for young male PD patients, who are felt most likely to exhibit PG. In addition, retrospective identification of mood disorders, substance misuse, and previous gambling may be biased in case control studies, and underestimated in studies where these behaviors are not actively sought. Only large prospective studies can overcome these limitations.

Risk Factors of Pathological Gambling in Parkinson's Disease

PG occurs as a rare side effect of treatment of PD in up to 8% of patients on DA. This prevalence is considerably higher than that in the general population, where the prevalence of PG is around 1%.[14] Patients are predominantly male and young. Psychiatric comorbidity was often present but as many studies were retrospective, it is not clear whether this is a predisposing factor or consequence of the condition. These findings are consistent with population-based observations that link PG to younger age, male gender, and high rates of psychiatric problems.[36] However substance misuse appears to be a less frequent risk factor in PD patients compared with PG in the general population. The majority of patients have no history of gambling or substance misuse. This may however be an underestimate as the majority of

studies did not actively screen for these premorbid risk factors.

Relationship to Dopaminergic Treatment

With the exception of one patient on selegiline and two on L-dopa alone, all the affected patients were on DA (98.3%). An initial case series of 12 patients[37] implicated L-dopa as a potential etiological agent for PG. However other dopaminergic drugs used (particularly DA) were not listed. Subsequently, several series reporting the phenomenon of DA-associated PG were published. Results of this analysis confirm treatment with this drug group as the largest independent risk factor. It has been suggested that the DA pramipexole is associated with a particularly increased risk of PG. Evidence for this includes a high adjusted reporting ratio compared with other DA in an FDA audit of adverse events.[38] However, the increased reporting ratio may reflect reporting bias in the FDA audit as the first large case series implicated pramipexole as the main etiological agent.[7] The difference may also reflect the relative prescription frequency of pramipexole (overall 43.6%, and >50% of DA prescriptions in several reported series[8,11]). Comparison of the risk of PG on different DA did not reach statistical significance, comparing pramipexole to ropinirole and comparing nonergot and ergot DA. With further prospective studies these differences may become significant; however the OR is likely to remain small.

The doses of DA were generally large, with a large proportion of patients taking higher than the recommended maximum dose, particularly of pramipexole. The use of L-dopa in the majority of PG patients may suggest cross-sensitization of brain systems mediating reward. This is further supported by the observation that many individuals with PG had been on stable doses for many months before PG evolved. However, many patients with PD are exposed to a large variety of different dopaminergic drugs and only a relative minority develop compulsive behaviors, indicating that individual factors, including a neurobiological predisposition, are highly relevant.

Neurobiological Predisposition

Ventromedial prefrontal cortex (VMPFC) involvement has been implicated in ICD from imaging studies. These include an fMRI study of individuals with PG (non-PD) compared with controls, which showed negative correlation between activation of the VMPFC and ventral striatum (an area implicated in drug addiction) and gambling severity.[39] PET studies in PD patients, unmedicated and with early stage disease, showed significantly lower activation in the orbitofrontal cortex (OFC) and amygdala, as well as striatum[40] and a further PET study in medicated PD patients performed while doing the Iowa Gambling task[41] showed reduced activity in the mesial-frontal areas.[42] Decreased activity of the OFC has been consistently reported in imaging studies of drug-addicts[43] and is consistent with evidence that the prevalence of PG is higher in addicts in general.[44] In DDS, PET studies have demonstrated sensitization of ventral striatum (VS) to dopaminergic transmission, which correlates with the trait of L-dopa "wanting".[45] VS sensitization is replicated in PET studies after amphetamine administration.[46] PG and chemical addiction share many similarities, which include difficulty in controlling the impulse to gamble/overuse medication and the persistence in these behaviors despite negative consequences. Investigation into the biological features of both PD and non-PD subjects with impulse control behavior provide support for at least an overlapping biological substrate.

Relationship to Impulse Control Disorders and Dopamine Dysregulation Syndrome

The patient characteristics of PG in PD are comparable to case series of other impulse control disorders in PD such as hypersexuality.[47] PG also shares a number of characteristics of DDS, such as male sex, early age of onset of PD, higher prevalence of depression than controls and intake of relatively high doses of DA. However, a number of patients with PG have been specifically reported not to have DDS and, conversely, not all patients with DDS have PG as part of the syndrome. PG also differs from DDS in that DA use is almost invariably associated (98.3%), whereas DDS is associated with high doses of L-dopa. In patients with PG, those with DDS have longer disease duration and higher total LEDD.

There are various hypotheses for the etiology of dopaminergic medication associated compulsive behaviors in PD. It may be speculated that differences between occurrence of DDS and PG are due to the shorter duration of action of L-dopa producing more instant effects than DAs in DDS, whereas PG may be an adverse effect relating to more continuous dopamine receptor stimulation. However, it is possible that PG represents a dose-dependent side effect of DA treatment with a different pathophysiology to DDS and overlap with the DDS phenotype may represent DA co-prescription in this group. The relative selectivity of DA for D3 dopamine receptors, including in mesolimbic areas of the brain, has been postulated as a mechanism for their association with impulse control disorders.[15] The differential receptor profile of L-dopa and DA (including differences be-

tween ergot and non-ergot DA) may influence the type of compulsive behavior that manifests.

Management

A large proportion of patients with PG were taking higher than the maximum licensed dose of DA. This should clearly be avoided, even with good antiparkinsonian benefit. Premorbid gambling, drug use histories, and impulsive sensation-seeking personality traits may be relevant in identifying at-risk individuals. The onset of PG may also occur after the introduction of new dopaminergic medications (particularly DA) or dose increases, and at these times, and especially in young male patients, particular attention should be given to the possibility of this syndrome, although overall only a relatively small minority of patients will be affected. In the non-PD population, there is evidence of benefit from cognitive behavioral therapy[48]; however long term compliance with self-help groups,[49] particularly in those with comorbid psychopathology or drug dependency, is poor. SSRI use has also been shown to be potentially beneficial.[50] In PD several treatment strategies have been reported to be beneficial but no prospective study has been conducted to date. Reduction of DA dose, possibly with increase in L-dopa to alleviate worsening PD symptoms, reduction of all dopaminergic treatments, or switching from one DA to another may be successful. However, changes to dopaminergic treatment are often not well tolerated and the psychological/cognitive treatments and psychotropic medication, used in the non-PD PG population may prove beneficial.

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