The four As associated with pathological Parkinson disease gamblers: anxiety, anger, age, and agonists

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Abstract: Several studies have related pathological gambling in PD to dopamine agonist therapy. A mail-in survey was sent to PD patients seen at the University of Florida Movement Disorders Center to determine gambling frequency and behavior, and any lifestyle or environmental factors associated with compulsive gambling in PD. 462 surveys were sent and 127 completed surveys were returned, of which ten were from patients who met criteria for compulsive gambling. All ten were taking dopamine agonists coincident with the compulsive gambling. Compulsive gamblers were younger, and psychological distress measures revealed that compulsive gamblers exhibited higher levels of anxiety, anger, and confusion. Thus in this cohort, we have uncovered the several characteristics of the most likely PD compulsive gambler, namely: (young) age, "angry", "anxious", and using a (dopamine) agonist.

Keywords: Parkinson, gambling, compulsive behavior, dopamine agonist, anxiety

Introduction

Parkinson's disease (PD) is a progressive, degenerative neurological disorder resulting from the destruction of dopaminergic neurons in the substantia nigra (Samii et al 2004). In addition to motor dysfunction, neuropsychological deficits in PD patients have been described, including deficits in decision-making (Giovannoni et al 2000), learning deficits (Swainson et al 2000), reinforcement learning (Frank et al 2004), goal-setting (Meiran et al 2004), and the performance of repetitive behaviors (Kurlan 2004; Samii et al 2004). In recent years, several studies have uncovered a subpopulation of patients with PD exhibiting signs of pathological gambling (Molina et al 2000; Seedat et al 2000; Gschwandtner et al 2001; Driver-Dunkley et al 2003; Avanzi et al 2004; Kurlan 2004; Dodd et al 2005). These studies reported that patients experienced an increased urge to gamble and were often unresponsive to typical treatments for pathological gambling, but were responsive to an adjustment in PD medications. Several studies have reported the onset of gambling behavior to be associated with external factors such as proximity of casinos and gambling facilities, and an increase in dopamine agonist medication, (more commonly pramipexole and ropinirole) (Molina et al 2000; Seedat et al 2000; Driver-Dunkley et al 2003; Dodd et al 2005) or other Parkinson's medications (Gschwandtner et al 2001; Avanzi et al 2004). However, some studies did not find a significant correlation of pathological gambling in PD with anti-Parkinsonian medication (Kurlan 2004).

To date the cause of pathological gambling in PD and the "phenotype" of the 'at risk' PD patient remain unclear. The inability of PD patients to successfully navigate gambling tasks could be contributing to the abnormal behavior. This supposition is supported by studies that have correlated dopamine levels during gambling (Bergh et al 1997; Shizgal and Arvanitogiannis 2003), specifically the fact that dopamine is released from the ventral striatum during the expectation of an uncertain reward

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(Zald et al 2004). It is unclear whether external factors such as dopaminergic medication or intrinsic factors underlying disease progression, or a combination result in pathological gambling in PD.

A survey of the patients with PD residing in North-Central Florida was performed to determine: gambling frequency and behavior; any iatrogenic and environmental factors associated with compulsive gambling in PD; and the presence of intrinsic factors associated with compulsive gambling in PD patients.

Methods

A mail-in survey was sent to all patients of the University of Florida Movement Disorders Center (where diagnosis of "probable" PD was made by a fellowship trained movement disorders specialist, using known criteria (Hughes et al 1992)) was performed. The protocol was approved by the local Institutional Review Board. Participants were not paid for their participation. This survey consisted of a demographic data questionnaire (including age, gender, duration of PD, medications, and questions about lifestyle), the State-Trait Anxiety Inventory (STAI), a Visual Analog Mood Scale (VAMS), the Neuropsychiatric Inventory, Beck's Depression Inventory-II (BDI-II), and a questionnaire on gambling and other compulsive behaviors (see Table 4). Items on the gambling survey were based on the DSM-IV criteria for pathological gambling and on a questionnaire provided by Gambler's Anonymous. The survey was anonymous with an option for the participant to provide us with his or her name and contact information for further participation in the research.

All subjects were grouped into one of three groups: compulsive gamblers (CG), non-compulsive gamblers (NCG), and non-gamblers (NG). CG were defined as subjects who answered affirmatively to at least four of the questions on the gambling survey derived from the DSM-IV or Gambler's Anonymous that indicated compulsive gambling behavior. NCG were defined as subjects who admitted to regularly engaging in gambling behavior, but whose responses on the gambling survey did not indicate compulsive gambling behavior. NG were defined as subjects who claimed to not engage in regular gambling behaviors.

For the data analysis, frequency distributions (eg, medication status and gender) were compared using χ^2 test. Most continuous variables (eg, age, illness duration, and most scores on the mood measures) were compared using analysis of variance (ANOVA) followed by Bonferroni post-hoc tests for significant results.

Results

A total of 462 surveys were mailed to PD patients in the North-Central Florida region, of which 182 were returned: 127 complete and 55 incomplete surveys. Only completed surveys were used in the analysis of this study. Of the 127 completed surveys, 10 (7.87%) were from PD patients who met criteria for CG; 27 (21.26%) PD patients were classified as NCG; 90 (70.87%) PD patients did not engage in regular gambling behaviors.

Demographic characteristics

The main characteristics of the three groups are shown in Table 1. The CG group was significantly younger than the NG group ($F\ [2,124] = 6.64$, $p < 0.01$). The three groups did not differ significantly in race composition, gender composition, or illness duration. There were more participants in CG group currently engaging in smoking behaviors ($\chi^2\ [2] = 23.17$, $p < 0.001$). However, the three groups did not differ significantly in the prevalence of alcohol use. There were no differences between groups in employment status (currently employed or retired), or stability of income source (fixed or not fixed).

Medication status

Table 2 shows medication status of the three groups. Compared with both the NG and the NCG groups, the CG group had significantly more participants who were taking dopamine agonist medications when they were reportedly experiencing compulsive gambling behavior compared with the NG ($\chi^2\ [1] = 8.38$, $p < 0.005$) and the NCG group ($\chi^2\ [1] = 4.41$, $p < 0.05$]. The NCG and NG groups did not differ significantly in number of participants who took dopamine agonist mediations [$\chi^2\ (1) = 1.76$, $p = 0.19$]. The three groups did not differ significantly in incident of current treatment with levodopa, anticholinergics, amantadine, monoamine oxidase-B (MAO-B) inhibitors, catechol-O-methyl transferase (COMT) inhibitors or other medications (see Table 2).

Regarding the use of psychiatric medications, more participants in the CG group were under tricyclic anti-depressant treatment compared to the NG and the NCG groups ($\chi^2\ [2] = 11.79$, $p < 0.005$). The three groups did not differ significantly in incident of current treatment of other antidepressants, or other psychiatric medications (see Table 2).

Table 1 Demographic data of all participants

Variable	Participants		
	CG	NCG	NG
N	10	27	90
Age (SD)	58.7 (13.7)a	66.6 (9.1)	69.4 (8.4)
% Caucasian	100.0	100.0	92.0
% male	80.0	81.5	58.9
Illness duration (SD)	7.8 (5.7)	10.0 (7.5)	7.8 (7.3)
Side onset			
% right	40.0	51.9	43.7
% left	30.0	37.0	42.5
% bilateral	20.0	3.7	6.9
% unsure	10.0	7.4	6.9
% currently smoking	20.0[b]	0.0	0.0
Alcohol use			
% use daily	10.0	11.1	14.4
% use occasionally	40.0	51.9	30.0
% never use	50.0	37.0	55.6
% retired	88.9	77.8	86.4
% with fixed income	90.0	81.0	81.5
Marital status			
% currently married	80.0	92.4	82.0
% never married	0.0	3.8	1.1
% separated	10.0	0.0	1.1
% divorced	10.0	3.8	10.2
% widowed	0.0	0.0	5.6

Note: [a]$p < 0.05$ vs NCG and NG; [b]$p < 0.001$ vs both NCG and NG.
Abbreviations: CG, compulsive gamblers; NCG, non-compulsive gamblers; NG, non-gamblers.

Personal and family psychiatric history

Statistical analysis of personal and family psychiatric history is listed in Table 3. There was no significant difference between groups in prevalence of personal psychiatric diagnoses (χ^2 [2] = 2.347, p = 0.31). Although a positive alcoholism history was more common among CG participants (χ^2 [2] = 11.79, $p < 0.005$), only one person (who happened to be in the CG group, giving a 10% prevalence) in the entire cohort reported a positive alcoholism history. There was no significant difference between groups in prevalence of psychiatric history in the family.

Psychological distress measures

The mean Beck Depression Inventory-II total score did not differ significantly between groups. The CG group obtained significantly higher score (representing greater degree of illness) on the *state anxiety* subscale [measuring current degree of anxiety] of the State-Trait Anxiety Inventory than the other two groups (F [2,123] = 4.30, $p < 0.05$). The CG group also demonstrated significantly higher scores on the *trait anxiety* subscale (measuring pervading anxiety) of the State-Trait Anxiety Inventory compared with the NG group, but not the NCG group (F [2,119] = 3.10, $p < 0.05$). On the VAMS, the CG group obtained significantly higher scores on the "confused" item than NG group (F [2,120] = 6.46, $p < 0.005$); there were no significant differences between the CG and the NCG groups or the NG and the NCG groups. Since we did not perform objective cognitive measures in this study, it was difficult to ascertain further what 'confusion' meant. In addition, the CG group demonstrated significant higher scores on the "afraid" subscale compared to the NG group (F [2,119] = 3.41, $p < 0.05$). There were no significant group difference between the CG and NCG groups as well as between the NCG and the NG groups. The CG group also obtained significantly higher scores on the "angry" subscale compared to the NG and the NCG groups (F [2,120] = 5.49, $p < 0.01$). There were no significant differences between groups on other items on the VAMS. The three groups did not differ significantly in the status of libido.

Gambling behaviors

Several types of common gambling behaviors were included in the survey. The analyses showed that the CG and the NCG groups did not differ significantly on prevalence of

Table 2 Medication data of all participants

Variable	Participants		
	CG	NCG	NG
% taking dopamine agonists	100.0[b,c]	66.7	52.2
% taking levodopa	90.0	88.5	75.6
% taking anticholinergics	0.0	3.7	1.0
% taking amantadine	0.0	14.8	8.9
% taking MAO inhibitors	20.0	33.3	8.9
% taking comt inhibitors	0.0	11.1	21.1
% taking SSRIs	20.0	18.5	6.7
% taking tricyclics	10.0[a]	0.0	0.0
% taking other antidepressants	20.0	33.3	28.9
% taking anxiolytics	10.0	29.6	12.2
% taking antipsychotics	10.0	25.9	10.0
% taking other psychiatric medications	30.0	14.8	22.2
% taking other medications	0.0	7.4	4.4

Note: [a]$p < 0.005$ vs NG and NCG; [b]$p < 0.005$ vs NG; [c]$p < 0.05$ vs NCG.
Abbreviations: CG, compulsive gamblers; MAO, monoamine oxidase; NCG, non-compulsive gamblers; NG, non-gamblers; SSRI, selective serotonin reuptake inhibitor.

engaging in different gambling behaviors, including state lottery, scratch-off tickets, slot machines, dog/horse track, casinos, cards (poker, blackjack, etc), and other gambling behaviors. In the CG group, 60% of people engaged in more than one gambling behavior; in the NCG group, 59.3% of people engaged in more than one gambling behavior. The most common gambling behavior in the CG group was "slot machines" (70%), followed by "scratch-off tickets" (50%), "cards" (40%), "state lottery" (30%), "casinos"(30%), and "dog/horse track" (20%). In the NCG group, the most common gambling behavior was "cards" (55.6%), followed by "state lottery" (51.9%), "slot machines" (48.1%), "scratch-off tickets" (33.3%), "casinos" (29.6%), and "dog/horse track" (11.1%).

Discussion

Use of a dopamine agonist medication and younger age were significant for the CG group in this study. However, this result may be confounded by the standard practice of using dopamine agonists in younger patients (Unwin et al 2000). Dopamine agonists are prescribed more often in younger patients primarily to delay the use of levodopa, and prevent early motor fluctuations and dyskinesias (Destee 2005; Jankovic 2005; Moller et al 2005).

Table 3 Personal psychiatric history and psychiatric history in the family

Variable	Participants		
	CG	NCG	NG
% any personal psychiatric history	40.0	37.0	24.4
% personal depression history (out of N)	20.0	29.6	21.1
% personal anxiety history	0.0	18.5	8.9
% personal bipolar disorder history	0.0	3.7	0.0
% personal OCD history[#]	10.0	0.0	1.1
% personal alcoholism history	10.0[a]	0.0	0.0
% with > one personal psychiatric history (among people with any psychiatric history)	0.0	30.0	22.7
% *any* family psychiatric history	30.0	33.3	36.7
% family depression history (out of N)	10.0	18.5	26.7
% family anxiety history	0.0	3.7	5.6
% family bipolar disorder history	10.0	3.7	8.9
% family OCD history	10.0	3.7	1.1
% family alcoholism history	10.0	14.8	13.3
% with > one family psychiatric history (among people with any family psychiatric history)	33.3	22.2	33.3

Note: [a]$p < 0.005$ vs NG and NCG.
Abbreviations: CG, compulsive gamblers; NCG, non-compulsive gamblers; NG, non-gamblers OCD, obsessive-compulsive disorder.

Our data corroborates other studies that have linked compulsive gambling in PD to dopamine agonist medication (Molina et al 2000; Seedat et al 2000; Gschwandtner et al 2001; Driver-Dunkley et al 2003; Avanzi et al 2004; Dodd et al 2005). There has been one previous study which reported compulsive gambling behavior in PD that was reported not to be related to PD medications (Kurlan 2004). However, both patients reported in that study were taking pramipexole, and while the authors stated that the patients' gambling behavior did not resolve with discontinuing the medication, the authors failed to note the length of a washout period was employed. Other studies have reported that the latency of resolution of gambling behavior following discontinuing dopamine agonist medication could four or more weeks (Dodd et al 2005). Finally, there are at least two other studies that have been unclear as to how long the behavior persisted following medication discontinuation (Gschwandtner et al 2001; Driver-Dunkley et al 2003).

Dopamine agonists enhance the functioning of endogenous dopamine, and non-specific action of the agonists may also influence non-motor basal ganglia loops, including the nucleus accumbens, mesolimbic/mesocortical circuits, and the anterior cingulated loop (Clarke and Guttman 2002). It has been theorized that dopamine agonists stimulate compulsive gambling behavior by selectively stimulating the D_3 receptor, which have been shown previously to be localized to the limbic regions of the brain (Alexander et al 1990). Other studies have shown that pramipexole and ropinirole, the two dopamine agonists that are most often associated with compulsive gambling, are relatively selective for the D_3 receptor (Dodd et al 2005). Finally, there is a literature suggesting that defects in the D_2 dopamine receptor are linked to pathological gambling (Sokoloff et al 1990; Comings et al 1996; Noble 2000).

Gambling in this cohort was found to be more common among men than women, and this was consistent with the literature (Unwin et al 2000). Also in agreement with other studies, compulsive gambling among PD patients also seems to be more common among men—other studies have reported men composed 7 of 9 and 9 of 11 PD compulsive gamblers, respectively (Driver-Dunkley et al 2003; Dodd et al 2005). Contrary to previous studies on compulsive gambling in the general population (Levens et al 2005), neither family history of alcoholism nor depression was a significant predictor of compulsive gambling behavior. This result will need to be confirmed by larger and better constructed studies.

"Anxious", "afraid", "angry", and "confused" were the four moods reported by the State-Trait Anxiety Inventory and VAMS found to be significant for the CG group. We primarily used the VAMS to probe into emotions such as anger and anxiety. "Anxious" and "afraid" could be describing the same emotion. However, we are more comfortable with "anxious" because we have more anxiety scales that support it; indeed, a follow-up of this study involves the

Table 4 Scores on psychological distress measures

	Participants					
	CG		NCG		NG	
Measure	**M**	**(SD)**	**M**	**(SD)**	**M**	**(SD)**
Beck Depression Inventory-II	16.1	(8.0)	9.9	(5.8)	11.7	(8.6)
State-Trait Anxiety Inventory						
State anxiety	46.4[a]	(10.6)	35.3	(10.8)	35.1	(11.9)
Trait anxiety	45.3[b]	(12.0)	36.0	(11.0)	35.5	(12.0)
Visual Analog Mood Scale						
Afraid (T score)	65.2[b]	(15.5)	54.1	(10.3)	54.0	(13.4)
Confused (T score)	64.9[c]	(16.6)	57.9	(15.2)	51.7	(11.2)
Sad (T score)	63.7	(19.9)	56.0	(18.2)	53.4	(13.2)
Angry (T score)	67.4[a]	(18.3)	55.1	(13.9)	53.5	(11.3)
Energetic (T score)	46.6	(10.8)	43.6	(10.4)	45.0	(11.4)
Tired (T score)	56.6	(10.1)	54.9	(10.0)	53.7	(11.2)
Happy (T score)	43.0	(12.9)	40.0	(13.6)	42.7	(11.7)
Tense (T score)	59.0	(9.7)	55.0	(12.2)	54.3	(12.8)
Libido status						
% no change	33.3		33.3		58.8	
% lower	44.5		47.6		33.8	
% higher	22.2		19.1		7.4	

Note: [a]$p < 0.05$ vs NG and NCG; [b]$p < 0.05$ vs NG; [c]$p < 0.01$ vs NG.
Abbreviations: CG, compulsive gamblers; NCG, non-compulsive gamblers; NG, non-gamblers OCD, obsessive-compulsive disorder.

administration of the Hamilton Anxiety Scale. "Confusion" is a vague term and could indicate cognitive impairment, guilt, frustration, disbelief, etc. While our limited survey does not reveal why our PD patients are experiencing such emotions, screening for these mood states may indicate which patients are most likely to experience pathological gambling as a result of dopamine agonist medication. However, as these are self-report measures, without corresponding objective cognitive and emotional measures, the conclusions that can be drawn from some of the VAMS items such as "confused" and "afraid" are limited.

Other studies have reported that compulsive gamblers with PD have noted "never experiencing anything like [compulsive gambling] before," and that such behavior was quite unusual for them and could not be explained (Dodd et al 2005). However, a higher prevalence of psychiatric/mood symptoms, in particular anxiety, in problem gamblers is to be expected (Petry et al 2005; Pietrzak et al 2005). Previously, compulsive gambling in PD has been associated with an increased sex drive (Dodd et al 2005), and other studies have shown that increases in sexually risky behavior may be associated with gambling, as both are risk-taking behaviors (Martins et al 2004). On the contrary, our study revealed that of the ten CG, four reported decreases in libido, and only two reported increases. A loss of libido may be an age-related change.

Admittedly, there are weaknesses to the study. First, as the survey was completed on a voluntary basis, the study lends itself to underreporting of the actual prevalence of compulsive gambling in PD in North Central Florida. Patients may be unwilling to disclose such private information in an impersonal manner. In addition, there may be a geographical bias in selecting for compulsive gamblers. North Central Florida is particularly devoid of casinos or other gambling establishments. It has been previously supposed that proximity to casinos may contribute to the development of compulsive gambling behavior in PD patients (Driver-Dunkley et al 2003). The prevalence of compulsive gambling in this region therefore may underreport the prevalence of compulsive gambling in regions with abundant gambling facilities. Unfortunately, we cannot verify the accuracy or truthfulness with which patients responded to the survey. This is an inherent flaw in using self-report measures. In addition, many patients may not consider their behavior irrational, or that they have a gambling "problem." Such patients may not have been truthful with their responses, or may not have returned a survey. Furthermore, with the limited number of participants who seemingly exhibited compulsive gambling behavior (ten), the conclusions that can be drawn from the data are equally as limited. The relevance and significance of this study must be evaluated in the context of other current and future studies regarding pathological gambling in Parkinson's disease.

Summary

In this survey, we have recognized several characteristics that may help identify which PD patients may be the most "at risk" for developing compulsive gambling behavior: young age, high degree of anxiety and anger, and use of a dopamine agonist. All patients that were suspected of compulsive gambling behavior were contacted, informed of the recent studies linking compulsive gambling and antiparkinsonian medications, and advised to speak to their physician. Future goals of this study are to conduct six-month and one-year follow-ups on the identified compulsive gamblers to observe if they have sought help for their behavior, and if their symptoms become resolved, what interventions were made to affect such a change. In the meantime, clinicians should be aware of these characteristics associated with pathological gambling and be particularly vigilant when treating this sub-population of PD.

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