

# The Risky Business of Dopamine Agonists in Parkinson Disease and Impulse Control Disorders

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Risk-taking behavior is characterized by pursuit of reward in spite of potential negative consequences. Dopamine neurotransmission along the mesocorticolimbic pathway is a potential modulator of risk behavior. In patients with Parkinson's disease (PD), impulse control disorder (ICD) can result from dopaminergic medication use, particularly dopamine agonists (DAA). Behaviors associated with ICD include hypersexuality as well as compulsive gambling, shopping, and eating, and these behaviors are potentially linked to alterations to risk processing. Using the Balloon Analogue Risk Task, we assessed the role of agonist therapy on risk-taking behavior in PD patients with ( $n = 22$ ) and without ( $n = 19$ ) active ICD symptoms. Patients performed the task both "on" and "off" DAA. DAA increased risk-taking in PD patients with active ICD symptoms, but it did not affect risk behavior of PD controls. DAA dose was also important in explaining risk behavior. Both groups similarly reduced their risk-taking in high compared to low risk conditions and following the occurrence of a negative consequence, suggesting that ICD patients do not necessarily differ in their abilities to process and adjust to some aspects of negative consequences. Our findings suggest dopaminergic augmentation of risk-taking behavior as a potential contributing mechanism for the emergence of ICD in PD patients.

*Keywords:* impulse control disorders, dopamine agonists, Parkinson's disease, risk behavior

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Risk-taking describes a decision or an action that creates an opportunity for reward while risking potential exposure to negative consequences (Jackson, Hourany, & Vidmar, 1972; Leigh, 1999). Taking risks in the pursuit of rewarding experiences is an essential aspect of human decision-making. Eating an extra slice of cake, while immediately rewarding to the palate, risks stomach discomfort. Yet some risks carry even greater potential for harm; for

example, speeding through a red stoplight in heavy traffic is a risky decision with potentially devastating consequences.

Recent imaging studies have associated risk-taking behavior with dopamine neurotransmission along mesocorticolimbic pathways (Lee et al., 2009; Rao, Kordzykowski, Pluta, Hoang, & Detre, 2008; Rao et al., in press). Variations in dopamine release are associated with the processing of both anticipated and actual action consequences. More precisely, phasic dopamine release is proposed to convey information about the incentive salience of a stimulus, the anticipated reward of an action, the actual reward, and prediction errors that represent the mismatch between expected and actual rewards (Berridge, 2007; Fiorillo, Tobler, & Schultz, 2003). In contrast, suppression or "pauses" in phasic dopamine activity appear to signal both the anticipation and experience of a "less than desired" or negative outcome, as well as the omission of an expected reward (Frank, Seeberger, & O'reilly, 2004). These findings suggest that the weighing of the probability of reward against potential negative consequences that is inherent to risk-taking may crucially depend on dopamine signaling in anticipation of the risk outcome and at the moment the outcome of a risky choice is experienced (Sanfey & Chang, 2008; St Onge, Chiu, & Floresco, 2010).

Alterations to dopamine neurotransmission along mesocorticolimbic pathways may impact risk-taking behavior. Parkinson's disease (PD) and its treatment provide a unique opportunity to

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investigate this hypothesis directly as a core pathological feature of PD is degeneration of dopamine producing neurons of the substantia nigra compacta and ventral tegmental area (Fearnley & Lees, 1991). The depletion of dopamine in PD produces initial changes in motor functioning, including resting tremor, bradykinesia, postural instability, and muscle rigidity, and has also been linked to early cognitive and mood changes. In PD, the dopamine neurons forming the nigrostriatal pathway are the earliest to degenerate and are largely responsible for the motor and early cognitive deficits (Hughes, Daniel, Kilford, & Lees, 1992; Merims & Freedman, 2008). In contrast, ventral tegmental area dopamine neurons comprising the mesocorticolimbic pathways remain relatively intact in early PD, with degeneration of these neurons typically emerging later in the disease course (Kish, Shannak, & Hornykiewicz, 1988). Pharmacological treatments for PD, although primarily aiming at restoring deficient dopamine levels, may “overdose” these relatively intact mesocorticolimbic pathways, thus biasing reward aspects of risk behavior and potentially diminishing sensitivity to negative consequences (Cools, Barker, Sahakian, & Robbins, 2001; Swanson et al., 2000).

This disruption to risk behavior may be especially pronounced when PD patients are treated with a dopamine agonist (DAA), which has a heightened affinity for D3 and D2 receptors expressed along mesocorticolimbic reward pathways (Black et al., 2002; Bostwick, Hecksel, Stevens, Bower, & Ahlskog, 2009; Dodd et al., 2005; Voon, Potenza, & Thomsen, 2007; Weintraub et al., 2010). A striking 15–20% of PD patients taking DAA develop clinical symptoms of impulse control disorder (ICD)(Voon et al., 2006; Weintraub et al., 2010). ICD is expressed in a number of behaviors, including hypersexuality, impulsive and compulsive shopping, pathological gambling, and compulsive hobbyism (Voon et al., 2007). Clinically, the toll of ICD can be devastating as patients exhaust their financial resources to gambling or shopping, compromise stable and supportive relationships to satisfy intense sexual urges, and neglect daily responsibilities while consumed for hours participating in hobbies (Voon et al., 2007). PD patients with ICD (PD-ICD) appear intensely drawn to highly rewarding experiences, but they may also discount or ignore the potential negative consequences of their decisions (Voon et al., 2010).

Empirical evidence that DAA directly alters risk-taking behavior in PD patients, particularly among those who develop ICD, would provide important clinical insight and further strengthen the hypothesized role of mesocorticolimbic dopamine in human risk behavior. In the current investigation, we studied 41 PD patients treated with DAA. Patients were further classified as those with ICD symptoms (PD-ICD,  $n = 22$ ) and those without ICD (PD controls; PD-C,  $n = 19$ ). A variant of the Balloon Analogue Risk Task (BART; Lejuez et al., 2002) was administered to patients on two occasions, during an “on” state (taking DAA medication) and an “off” state (DAA medication withdrawn). Recent imaging studies have shown that risk-taking in the BART is associated with activity in mesocorticolimbic structures as well as higher ratings of sensation-seeking and impulsivity on self-report questionnaires, frequencies of smoking, drug, and alcohol use, and rates of criminal activity (Hunt, Hopko, Bare, Lejuez, & Robinson, 2005; Lejuez, Aklin, Daughters, et al., 2007; Lejuez, Aklin, Jones, et al., 2003; Lejuez, Aklin, Zvolensky, & Pedulla, 2003; Rao et al., 2008).

We hypothesized that DAA would increase risk behavior, especially among PD patients who developed ICD clinically. Specifically, we predicted higher risk-taking in the BART in the DAA “on” compared to the DAA “off” state and that this pattern would be most pronounced for the PD-ICD group compared to the PD-C group. The BART was also designed to test the hypothesis that the increase in risk-taking due to DAA involves a reduced sensitivity to the anticipation or to the experience of negative consequences. Thus, patients in the “on” DAA state, and particularly those with ICD, would be expected to show less of a reduction in risk-taking both in a context in which the probability of negative consequences is relatively high and directly after experiencing a negative consequence. Finally, we examined the relationship between DAA dose and susceptibility to risk behavior, and predicted that patients taking a larger dose of DAA would show a pattern of increased risk-taking compared to patients taking smaller doses of DAA.

## Methods

### Participants

Forty-one individuals with both a clinical diagnosis of idiopathic PD and concomitant DAA use consisting of either pramipexole or ropinorole participated in this study. Twenty-six of the 41 patients were also taking levodopa cotherapy. All participants were recruited and evaluated at the Movement Disorders Clinic at the University of Virginia. A neurologist specializing in movement disorders confirmed the diagnosis of idiopathic PD, and motor symptom severity was graded using the Unified Parkinson’s disease Rating Scale (UPDRS) motor subscore obtained during each patient’s “on” medication state. Prior to entry into the study, patients’ medical histories were carefully reviewed, and they were screened for global dementia and major depression using the Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975) and Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), respectively. Patients were excluded if they had a history of comorbid neurological condition such as stroke, peripheral neuropathy, or seizure disorder; an untreated or unstable mood disorder such as major depression; dementia; history of bipolar affective disorder, schizophrenia, or other psychiatric condition known to compromise cognition; or an untreated or unstable medical condition known to interfere with cognition such as diabetes or pulmonary disease. All participants had normal or corrected-to-normal vision. Prior to study entry, participants provided informed consent, which was compliant with standards of ethical conduct in human investigation as regulated by the University of Virginia.

Patients were selectively recruited with current DAA use and screened for presence of ICD symptoms. All participants enrolled in the study were distinguished based on the presence or absence of ICD symptoms. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s disease (QUIP) was completed by patients and by a spouse or reliable informant (Weintraub et al., 2009). This instrument screens for the presence or absence of any of the primary ICD symptoms, including pathological gambling, compulsive buying, compulsive eating, and hypersexuality, and for secondary manifestations such as compulsive hobbyism, punting, and dopamine dysregulation syndrome. Patients and their infor-

ments were also interviewed to confirm that their behavior met established criteria for ICD behaviors (Voon et al., 2007) and that these behaviors were both disruptive to daily functions and temporally coincident with DAA therapy. Patients who did not meet criteria for any ICD symptoms were recruited as PD controls (PD-C), thus this was not a prevalence sample. None of the PD control patients acknowledged or met criteria for any ICD symptoms. DAA doses were converted to levodopa equivalent daily dose (LEDD) values (Weintraub et al., 2006).

### Experimental Task, Design, and Procedures

Patients completed a variant of the Balloon Analogue Risk Task (BART; Lejuez et al., 2002) on each of the two visits. For one visit, patients performed the task in an “on” state in which they were taking their DAA as regularly prescribed. For a second visit, they performed the task during an “off” state in which DAA medication had been withheld for at least 16 hours prior to the testing session. The order of visits with respect to DAA state was counterbalanced across patients and within PD-ICD and PD-C subgroups. Patients taking levodopa cotherapy remained on their current levodopa dosing schedule during both visits. Patients completed testing at similar times of the day for each visit.

The BART was administered using a PC computer and a 17-inch monitor positioned at eye level and located approximately 1 m in front of the participant. Participants sat in a comfortable chair and held a response grip in their preferred hand that registered a button press with the thumb. Participants were instructed that the goal of this task was to win as much money as possible. To accomplish this goal, participants were instructed to focus their attention on a box located at the lower, center portion of the screen (see Figure 1) and wait for a balloon to appear just above this box. They were told that the balloon would begin to inflate, and that each time it inflated, the value of the balloon would increase by 5 cents. The more that the balloon inflated, the higher the amount of money that was earned (e.g., 2 inflations = \$0.10; 6 inflations = \$0.30). Each inflation increased the balloon’s diameter by 4 mm, and balloons inflated at a rate of one inflation per second. Participants were told that they could cash the balloon at any time by pressing the response button, which would add the current value of the balloon to a virtual bank. For example, if the participant hit the cash button after 6 inflations of the balloon, \$0.30 would be added to their bank. Importantly, participants were told that a balloon could pop with each inflation of the balloon. If a balloon popped before the participant pressed the cash button, the value of that balloon would be lost and no money would be added to the bank. Money could only be added to the bank; it could never be removed (i.e., the bank represented a cumulative total amount of money earned from cashed balloons). Participants were instructed to maximize their earnings and were free to decide when to cash a balloon. Participants were not reimbursed for their total virtual earnings.

A trial consisted of a single balloon, and after a balloon was cashed or popped, a new trial began with the appearance and inflation of another balloon. To assist in their decision-making, three additional pieces of information were displayed on the screen at all times. First, the value of the current balloon was shown in the center of the balloon and a small box located to the lower left side of the screen (see Figure 1). This value began at \$0.00 for each

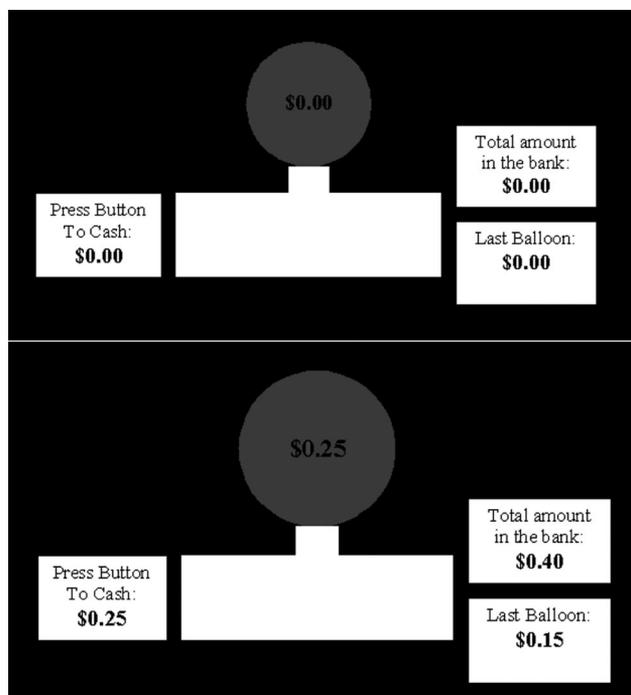


Figure 1. Two trial displays of the Balloon Analogue Risk Task.

new balloon and increased by increments of \$0.05 each time the balloon inflated. Second, a box positioned to the right of center side of the screen showed the cumulative amount of money that had been added to the virtual bank. This value was updated after each balloon was cashed or remained constant after a balloon popped. Finally, a box in the lower, right corner of the screen showed how much money had been earned on the previous balloon.

Participants first completed 10 practice trials to become familiarized with the rate of balloon inflations and to practice cashing balloons. Participants then completed two experimental rounds of 40 trials, with a short break (1–2 minutes) imposed between rounds. The two rounds differed on the basis of the risk of popping, which we termed the “risk context.” In the “Lower Risk” round, the probability that a balloon would pop on each inflation was 5%. In the “Higher Risk” round, each inflation of the balloon was associated with a 10% chance of popping. These differences in risk context were explained to the participant using an analogy of balloon quality. “Higher quality” balloons were associated with lower risk of popping each time the balloon inflated (Lower Risk context), whereas “lower quality” balloons were associated with a higher risk of popping with each inflation (Higher Risk context). Risk context was counterbalanced across testing sessions and participants. The exact probabilities for the two conditions were not provided explicitly. Unbeknownst to the participant, the optimal number of inflations to maximize earnings in the Lower Risk and Higher Risk conditions was 14 and 7 inflations, respectively.

The primary dependent measure was the average number of inflations risked on trials in which the patient cashed a balloon. This measure is sensitive to individual and group differences in risk preference and correlates positively with self-report measures

of sensation seeking and impulsivity as well as with high risk behaviors (Lejuez, Aklin, Zvolensky, et al., 2003). As a novel measure to assess how patients adjusted their risk behavior following popped balloons, we calculated the average number of inflations on cashed trials immediately preceding and immediately following a trial in which the balloon popped. We expected that fewer inflations would be risked after a popped balloon, suggesting a more cautious risk strategy following a negative consequence.

### Statistical Analysis

The data were analyzed using repeated-measures analysis of variance techniques with an alpha level set to 0.05. A first analysis included a between-subjects factor of ICD (PD-ICD, PD-C), along with within-subjects factors of Dopamine Agonist (off, on), and Risk Context (lower risk, higher risk). To further explore the role of DAA dose on risk behavior, we included an additional analysis that partitioned the entire sample of PD patients into three subgroups based on a tertile split of the rank-ordered total DAA LEDD equivalent. This analysis included a between-subjects factor of Agonist Dose (low, moderate, high) and within-subjects factors of Dopamine Agonist (off, on) and Risk Context (lower risk, higher risk). A planned contrast focused on the prediction that patients taking the highest DAA doses would show greater risk-taking behavior in the on DAA state compared to patients taking relatively lower doses.

### Results

We first present clinical characteristics of the study cohort. Then we show the effects of DAA (on vs. off), ICD status (PD-ICD, PD-C), and DAA dose (low, moderate, and high), on risk-taking behavior. Of note, session order (off-on agonist, on-off agonist) and levodopa cotherapy did not influence the pattern of results or interact with any experimental factors. The following results collapse across both session order and levodopa cotherapy. See the Supplemental Materials for these analyses.

#### Patient Characteristics

Of the 41 PD participants, 22 were identified with active symptoms indicative of ICD (PD-ICD) coincident with DAA use. Additionally, 19 patients were classified as PD controls (PD-C). PD-ICD and PD-C patients had similar clinical characteristics (see Table 1). ICD symptoms included hypersexuality (13/22), compulsive shopping or buying (12/22), compulsive eating (10/22), pathologic gambling (2/22), and compulsive hobbyism (17/22).

#### Analysis of Risk-Taking Behavior

Average inflations risked in each risk context are presented in Figure 2. Patients adjusted risk-taking according to the probability of negative consequences. On average, participants risked more inflations when the chance of the balloon popping with each inflation was lower compared to when it was higher (7.0 vs. 3.1), Risk Context,  $F(1, 39) = 203.9, p < .001$ . This pattern of risk adjustment was uninfluenced by either agonist state or ICD status, Risk Context  $\times$  Agonist State,  $F(1, 39) = 0.19, p = .66$ ; Risk Context  $\times$  ICD,  $F(1, 39) = 0.14, p = .71$ . Across patients the average number of inflations risked did not differ between “off”

Table 1  
*Parkinson's Disease (PD) Participant Characteristics*

Characteristic	All PD ( <i>N</i> = 41)	PD-ICD ( <i>n</i> = 22)	PD-C ( <i>n</i> = 19)
Age (years)	62.5 (6.9)	61.4 (5.5)	63.8 (8.1)
Education (years)	16.9 (2.5)	17.0 (2.3)	16.8 (2.8)
Gender (male:female)	22:19	13:9	9:10
MMSE	28.8 (1.5)	28.6 (1.8)	29.1 (0.9)
CES-Depression Score	10.9 (7.6)	12.9 (8.9)	8.6 (5.1)
Disease Duration (years)	8.1 (6.2)	9.7 (7.0)	6.1 (4.4)
UPDRS Motor Score	17.4 (7.8)	18.7 (7.2)	15.9 (8.4)
Patients on Agonist			
Monotherapy	15	7	8
Agonist Duration (years)	4.0 (3.5)	4.7 (3.8)	3.2 (3.1)
Levodopa Dose (mg)	415.9 (375.2)	444.25 (409.3)	383.2 (339.6)
Agonist Dose in LEDD (mg)	262.8 (146.4)	291.6 (160.5)	229.5 (124.0)
Total LEDD (mg)	678.7 (397.5)	735.8 (450.6)	612.6 (325.0)

*Note.* Values represent averages with standard deviations reported in parentheses. None of the comparisons between patients with ICD (PD-ICD) and PD controls without ICD (PD-C) were statistically significant. ICD = impulse control disorder; MMSE = mini-mental state examination; CES = Center for Epidemiological Studies; LEDD = levodopa equivalent daily dose.

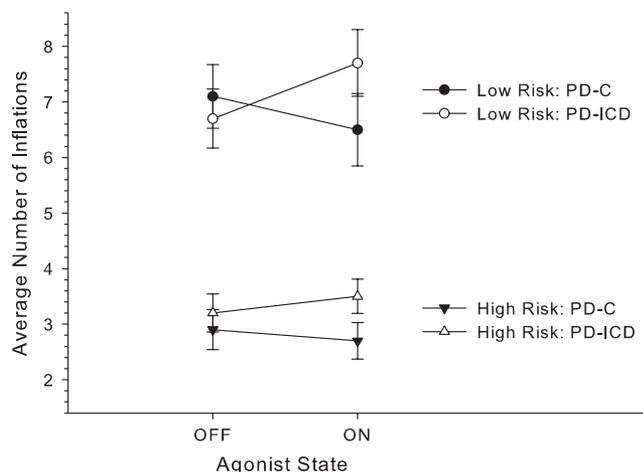
and “on” DAA states (5.0 vs. 5.1), Agonist State,  $F(1, 39) = 0.20, p = .66$ , or between PD-ICD and PD-C (5.3 vs. 4.8), ICD,  $F(1, 39) = 0.84, p = .37$ .

Importantly, agonist state selectively influenced the risk-taking behavior of PD-ICD compared to PD-C patients, Agonist State  $\times$  ICD,  $F(1, 39) = 5.59, p = .02$ . As depicted in Figure 2, the average inflations risked by PD-C and PD-ICD patients were similar in the “off” dopamine agonist state. However, in the “on” agonist state, PD-ICD patients significantly increased their average number of inflations risked as compared to PD-C patients, who showed a slight decrease in inflations risked. This pattern suggests that dopamine agonists induced riskier behavior in a subset of PD patients with active ICD symptoms. Notably, this pattern of increased risk-taking in PD-ICD patients in the “on” agonist state did not depend on the pop risk context, Agonist State  $\times$  ICD  $\times$  Risk Context,  $F(1, 39) = 1.34, p = .26$ .

#### Risk Adjustment After Negative Outcomes

We anticipated that patients would adopt a more cautious risk strategy on trials that followed a popped balloon. This predicted adjustment to negative consequences was measured by comparing the average number of inflations risked for cashed trials that immediately followed a popped balloon to cashed trials immediately preceding a popped balloon. This analysis included Agonist State (on, off), Risk Context (lower risk, higher risk), and Sequence (prepop, postpop) as within-subject factors, as well as ICD status (PD-ICD, PD-C) as a between-subjects factor. Here we focus on the Sequence effects, as the pattern of effects involving the remaining factors was unchanged from the above analysis.

Patients with and without ICD as well as “on” and “off” of their DAA medication reduced risk-taking similarly following negative outcomes (see Figure 3). Overall, patients risked fewer inflations on trials following a popped balloon (5.1) compared to trials preceding a popped balloon (5.9), Sequence,  $F(1, 39) = 65.25,$



**Figure 2.** PD control patients without ICD (PD-C) and patients with ICD (PD-ICD) show equivalent balloon inflations risked off dopamine agonist medication irrespective of risk context. When on DAA, PD-ICD patients show an increase in inflations risked compared to PD-C patients across both risk contexts. Error bars indicate standard error of the mean.

$p < .001$ . This post-pop adjustment in risk-taking depended on the pop risk context, Risk Context  $\times$  Sequence,  $F(1, 39) = 11.18$ ,  $p < .01$ ; that is, the reduction in inflations risked after a pop was greater in the lower risk condition compared to the higher risk condition. Importantly, the reduction in risk-taking following a balloon pop was not influenced by DAA state, ICD status, or their interaction (all  $ps > 0.10$ ).

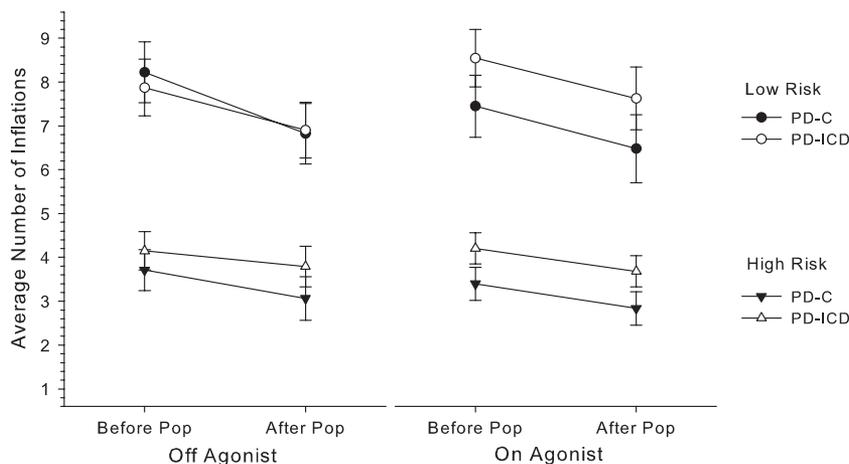
### Effects of Daily Dopamine Agonist Dose on Risk Behavior

All patients were subdivided into three equally sized groups based on DAA dose. Expressed in LEDD, 14 patients were taking low doses of a DAA (150 mg or less; range: 37.5–150), 13 moderate doses (range: 200–300 mg), and 14 high doses (375 mg

or higher; range: 375–600). The high DAA dose group had a higher ratio of PD-ICD to PD-C patients (10:4) as compared to the moderate (8:5) and low (7:7) groups, but these proportions were not statistically different ( $\chi^2 = 3.06$ ,  $df = 2$ ,  $p = .22$ ). Included in the analysis were within-subject factors of Agonist State (on, off) and Risk Context (lower risk, higher risk) as well as the between-subjects factor of Agonist Dose Group (low, moderate, and high; see Table 2). Here we focus on the Agonist Dose effect, as the main effects involving Agonist State and Risk Context remained unchanged from the above analyses. We predicted that there would be a specific interaction between Agonist State and Agonist Dose that would reveal a greater increase in risk-taking among patients taking relatively higher doses of DAA when on compared to off of their DAA.

Overall, the average inflations risked were similar across DAA dose groups (Low = 5.3, Moderate = 4.7, and High = 5.2), Agonist Dose,  $F(2, 38) = 0.52$ ,  $p = .60$ . However, DAA state differentially influenced risk-taking among the groups, Agonist State  $\times$  Agonist Dose Group,  $F(2, 38) = 6.78$ ,  $p < .01$ , and this effect was sensitive to the risk context, Agonist State  $\times$  Agonist Dose Group  $\times$  Risk Context,  $F(2, 38) = 3.76$ ,  $p = .03$  (see Table 2). In deconstructing this interaction, differences in risk-taking between the groups as a function of DAA state were significant only in the low risk context,  $F(2, 38) = 6.89$ ,  $p = .003$ , but not in the high risk context,  $F(2, 38) = 1.14$ ,  $p = .25$ . Figure 4 depicts the change in inflations risked between DAA states, on minus off, for each of the DAA dose groups under both high and low risk contexts. As the figure illustrates, the change in inflations risked in the low risk context was greater for patients taking higher doses of DAA compared to the low dose group,  $t(26) = -2.25$ ,  $p = .015$  (one-sided test with Bonferroni corrected  $\alpha = .017$ ) and moderate dose group,  $t(25) = -3.68$ ,  $p < .001$  (one-sided test). Patients taking moderate doses of DAA did not risk more inflations than patient taking lower doses in the low risk context,  $t(25) = 1.36$ ,  $p = .10$  (one-sided test).

The low dose DAA group had an equal proportion of PD-ICD and PD-C patients. We assessed changes in risk behavior for this



**Figure 3.** PD controls (PD-C) and PD patients with ICD (PD-ICD) showed a similar reduction in balloon inflations risked on trials following a popped balloon compared to trials preceding a popped balloon. This effect was independent of risk context and agonist state. Error bars indicate standard error of the mean.

Table 2  
Balloon Inflations in Dopamine Agonist Subgroups

Context	Low Dose (n = 14)		Medium Dose (n = 13)		High Dose (n = 14)	
	Off DAA	On DAA	Off DAA	On DAA	Off DAA	On DAA
Low Risk						
Context	7.6 (2.7)	7.5 (2.7)	6.9 (2.7)	5.8 (2.2)	6.1 (2.0)	8.0 (3.4)
High Risk						
Context	2.9 (1.1)	3.2 (1.2)	3.2 (1.8)	2.6 (1.4)	3.3 (1.9)	3.5 (1.9)

Note. Average number of inflations risked as a function of risk context (low vs. high) and dopamine agonist (DAA) state for PD subgroups based on agonist dose. Standard deviations are reported in parentheses.

group separately as an additional test of the hypothesis that patients with ICD possess a specific vulnerability to the effects of DAA on risk behavior. Specifically, we expected that the PD-ICD patients would still show increased risk-taking “on” DAA compared to the PD-C group despite the fact that both patient groups were taking lower doses of DAA. Using the change in inflations risked (on minus off DAA) as the dependent measure, we used a simple *t* test to compare these PD-ICD and PD-C subgroups. Since we established a directional prediction a priori, we used a one-sided hypothesis test. This analysis showed that PD-ICD patients in the low dose group risked more overall inflations “on” compared to “off” DAA (+0.8 inflations) than the PD-C patients, who tended to risk slightly fewer inflations “on” versus “off” DAA (−0.5 inflations),  $t(12) = -1.89, p = .04$ . This suggests that even among patients taking lower doses of DAA, those with ICD still showed a DAA-induced increase in risk-taking compared to those without ICD.

### Associations of Risk Behavior to Key Clinical Features of PD

We examined the association (Pearson correlation) between the change in inflations risked between “off” and “on” DAA states and the following set of clinical features: time on agonist, disease duration, motor symptom severity, and agonist dose in LEDD. After Bonferroni correction for multiple comparisons (adjusted *p* value = .006), no clinical features correlated with the change in inflations risked between “off” and “on” DAA states for either low or high risk contexts (all *ps* > 0.10). Notably, agonist dose (in LEDD) tended to modestly and positively correlate with inflations risked in the low risk context ( $r = .35, p = .02$ ), although this fell short of the adjusted significance *p* value. This trend, however, is consistent with the results obtained from the agonist dose subgroup analysis that indicated that, relative to patients taking lower doses of DAA, patients taking the highest doses increased risk-taking in situations where risk was less likely to be penalized (i.e., low risk context).

### Discussion

This study provides new evidence linking human risk-taking behavior to the dopaminergic system and dopaminergic pharmacotherapy in PD. Compared to the temporarily withdrawn DAA state, the acute on DAA state did not increase risk behavior across

patients globally, but it produced two selective effects. First, the on DAA state increased risk-taking in PD patients taking the highest doses of DAA compared to patients taking relatively lower doses. Second, the on DAA state increased risk-taking in patients who had developed clinical symptoms of ICD during DAA use but not in patients who had not developed ICD. These patterns suggest that the relationship between DAA use and risk-taking behavior in PD patients is potentially dose sensitive and linked to neurobiological vulnerabilities in the dopamine system.

Increased risk-taking may be driven by enhanced reward processing or diminished sensitivity to negative consequences. While our study design did not manipulate aspects of reward processing directly, the participants’ goal was to take risks to maximize reward. The finding that patients on high doses of DAA and with ICD increased risk taking while “on” DAA may result from an enhanced focus on rewarding aspects of their experiences (Voon et al., 2010). The effect of dopamine augmentation on reward-based learning is widely reported in the PD literature and is hypothesized to occur either as result of an alteration in dopaminergic tone or in the physiologic response to reward stimuli (Frank et al., 2004; Guthrie, Myers, & Gluck, 2009). Higher tonic levels of dopamine may amplify phasic dopamine bursts associated with reward signaling while concurrently attenuating pauses in dopamine phasic activity that signal the expectation or occurrence of negative consequences (Cools et al., 2001). As a result, patients may appraise outcomes as relatively “better than expected” under the dopaminergic “overdosing” influence of DAA (Cools et al., 2001; Voon et al., 2010). This theory, however, may not fully explain why ICD patients repetitively seek and engage in certain behaviors such as eating, shopping, or gambling. Alternatively, it has been proposed that compulsive reward-seeking behavior induced by chronic DAA use results from a “blunted” response to reward, which compels an individual to seek additional rewards as a

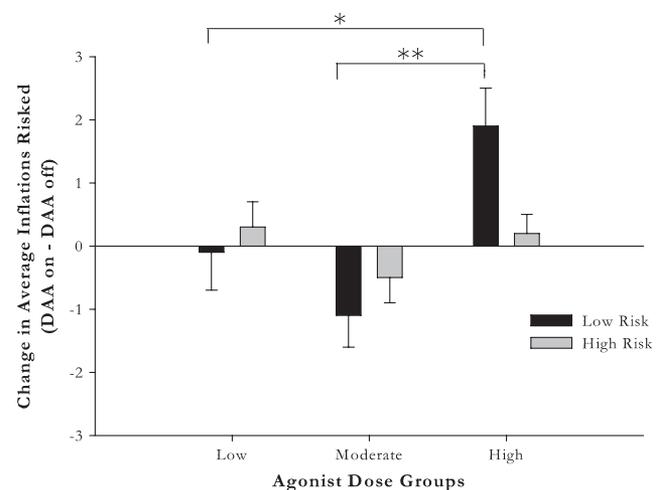


Figure 4. The change in average inflations risked when on compared to off dopamine agonist (DAA) medication for patients taking different doses of DAA. Positive values indicate higher risk-taking while on DAA. Compared to patients on low and moderate doses of DAA, patients taking a high dose of DAA significantly increased balloon inflations risked when on their DAA, particularly in low risk contexts. Error bars indicate standard error of the mean. \*  $p < .017$ . \*\*  $p < .001$ .

compensatory process to overcome inadequate reward feedback (Riba, Kramer, Heldmann, Richter, & Munte, 2008).

The processing of negative consequences is also an essential aspect of risk-taking behavior and decision-making. We assessed the possibility that PD patients taking DAA, and particularly those with ICD, are less sensitive to expected or experienced negative consequences. We accomplished this by manipulating the probability of negative consequences and measuring patients' adjustments in risk behavior following the occurrence of a negative outcome. Clinically, this is an important question, as ICD patients repeatedly engage in destructive behaviors, and it is possible that a disregard for punishment could explain why these are repeatedly engaged. Independent of DAA state, patients adopted a more cautious risk strategy in contexts where the risk of negative consequence (i.e., a balloon popping) was higher and increased risk-taking when the risk of negative consequences was lower. Patients with and without ICD made these adjustments similarly. Likewise, all patients, independent of DAA state and ICD status, were less risky on trials that followed a negative outcome. These results indicate that patients were able to adjust risk behavior on the basis of global expectations about negative consequences and following exposure to actual negative consequences. Moreover, these results do not support the conclusion that PD patients taking DAA, including those who develop ICD, show impaired processing of or adjustment to negative consequences. In a population of young participants with a history of previous stimulant use, Leland and Paulus showed that even though this population engaged in more risky decisions, they were more cautious after experiencing a punishment (Leland & Paulus, 2005).

It is important to note that while these relatively macro adjustments to negative consequences seem unaffected by ICD status and DAA state, it is still possible that the processing of negative consequences is altered by these factors. Specifically, each inflation carried with it the risk of losing a higher amount of accrued money for that balloon; thus, the increased risk-taking by ICD patients when on DAA may have been driven by stronger pursuit of reward or reduced concern about the increasing magnitude of the potential negative consequence associated with each inflation. Future work that systematically varies the ratio and magnitude of reward/punishment outcomes would be helpful for studying this within-trial, micro aspect of negative consequence processing.

Perhaps the most striking finding was that the DAA on state increased risk-taking behavior in a subset of PD patients who developed ICD clinically. Importantly, this increase in risk-taking did not depend on DAA dose directly, as even the PD-ICD patients taking the lowest doses of DAA showed increased risk-taking while on compared to off DAA compared to patients without ICD. In patients who did not develop ICD coincident with DAA use, risk-taking was equivalent in off and on DAA states. The finding that only patients with active ICD show changes in risk processing during the on DAA state is consistent with previous imaging and clinical studies suggesting that individual differences in mesocorticolimbic function may be critical for predisposing patients to risky behavior and the development of ICD symptoms (van Eimeren et al., 2009, 2010). For instance, patients with and without ICD show dissociable patterns of dopamine release and mesocorticolimbic activation during the performance of gambling or risk-taking tasks, even in the absence of behavioral differences in risk-taking (Rao et al., in press; Steeves et al., 2009; Thiel et al.,

2003; Voon et al., 2010). Moreover, clinical risk factors for developing ICD also suggest a propensity for risky behavior, including a history of gambling, substance use or abuse, and novelty-seeking behavior (Gallagher, O'Sullivan, Evans, Lees, & Schrag, 2007; Pontone, Williams, Bassett, & Marsh, 2006; Voon et al., 2007). Thus, DAA use may exacerbate or potentiate these neurobiological and behavioral vulnerabilities, resulting in alterations to reward and risk processing that drives clinical symptoms of ICD. Our results add behavioral support to the emerging view that the clinical expression of ICD reflects converging genetic, environmental, and pharmacological influences on dopamine and mesocorticolimbic function.

While these results highlight significant DAA-dependent changes in the risk behavior of ICD patients, there are certain extant issues and limitations worth noting. Regarding the BART, patients played for virtual monetary rewards instead of actual money, which may have reduced the strength of motivation or incentive salience for reward as well as decreased the level of concern for negative events. However, it is notable that all patients risked more inflations to obtain higher rewards when the probability of negative consequences was reduced, suggesting that participants were motivated to maximize reward. Additionally, patients risked fewer inflations on average than was optimally defined by the task. Since ICD patients showed an increase in risk-taking on DAA, it could be interpreted that these patients showed a more effective risk-taking strategy while on their medication. However, this interpretation is challenged by the fact that in previous studies of the BART, healthy adults typically risked fewer inflations than was optimally defined by the task, suggesting that suboptimal risk-taking may be more related to task factors than to individual differences (Lejuez et al., 2002). While this interpretation cannot be fully excluded by the present findings, the important pattern is that risk behavior was selectively altered by DAA state in this subset of patients with a known behavioral syndrome of risky and impulsive behavior.

Another limitation was that the probability of balloon popping remained constant across inflations, which does not mimic pop probabilities associated with the inflation of real-world balloons. This may have altered risk perception in a characteristic way that also changed risk-taking behavior. As discussed above, varying the reward and punishment magnitudes associated with each inflation could provide additional insights into the moment-by-moment weighing of potential outcomes that underlie risk decision-making.

While we also tested the potential impact of levodopa cotherapy and found no effects on risk-taking, future studies will need to address the role of levodopa separately. Levodopa therapy simulates endogenous dopamine production, and it is also rarely associated with behavioral side effects such as "dopamine dysregulation syndrome" and even ICD (Evans et al., 2004; Weintraub et al., 2010). Differences in the impact of these dopamine therapies on risk behavior could provide new insights into the mechanisms of ICD. Both the analysis of DAA dose groups and the modest correlation between dose and risk-taking in the low risk context suggested a potentially important relationship between DAA and risk processing. Although it was not statistically different, the high dose group included a higher ratio of PD-ICD to PD-C patients. The increased proportion of patients with ICD in the higher DAA dose group also suggests an association. However, it will be important to replicate a DAA dose effect on risk-taking in a larger

group of PD patients without ICD. Finally, even though the current results suggest that alterations in risk processing may be an important feature of ICD, disruption to other cognitive processes, including reward/punishment learning and inhibitory control, may contribute to the clinical syndrome of ICD (van Eimeren et al., 2009, 2010).

In summary, the current results reveal an important link between DAA use and risk-taking behavior, especially in a vulnerable subset of PD patients with active ICD. These patients did not show global reductions in sensitivity to negative consequences as they reduced risky decisions under conditions of higher risk and after experiencing negative consequences. The pattern of increased risk-taking may be driven by stronger pursuit of rewarding outcomes or by diminished concern for the potential for negative consequences at the moment a decision is made. Future work is needed to further characterize changes in reward and punishment processing in patients with active ICD. The increase in risk-taking induced by DAA offers a potentially novel explanation for the emergence of ICD symptoms in PD patients.

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## Supplementary Data

### Test Order Effects on Risk-Taking

To rule out the effects of testing order, we included Test Order (Off/On DAA vs. On/Off DAA) in addition to ICD status (PD-ICD, PD-C) as between-subjects factors along with Agonist State (Off, On) and Risk Context (Lower Risk, Higher Risk) as within-subject factors. Twenty-one patients completed the task first in the 'on' DAA state compared to twenty patients who started first in the DAA 'off' state. The analysis showed no impact of Test Order on average inflations risked,  $F(1,37)=0.08, p=0.77$ . In fact, patients who first completed the task in the DAA 'on' condition risked an average of 5.0 inflations, whereas patients first completing the study in the DAA 'off' condition risked an average of 5.1 inflations overall. Importantly, the effect of Test Order on inflations risked did not interact Agonist State,  $F(1,37)=0.11, p=0.74$ , nor with ICD Status,  $F(1,37)=0.57, p=0.45$ . None of the higher order interactions involving Test Order were statistically significant. Notably, the ratio of patients first taking the task in the DAA 'on' versus DAA 'off' state was similar between PD-ICD (11:11) and PD-C (10:9) groups, ( $\chi^2=0.46, df=1, p=0.50$ ).

### The Effects of Levodopa Co-Therapy on Risk-Taking

To examine the possibility that risk-taking was impacted by whether patients were taking levodopa in addition to DAA, we included Levodopa Therapy (No, Yes) in addition to ICD status (PD-ICD, PD-C) as between-subjects factors along with Agonist State (Off, On) and Risk Context (Lower Risk, Higher Risk) as within-subject factors. The analysis showed no impact of Levodopa Therapy on average inflations risked,  $F(1,37)=0.06, p=0.81$ . Overall, patients taking DAA plus levodopa therapy risked an average of 5.0 inflations, whereas patients on DAA monotherapy risked 5.1 inflations. Importantly, the effect of Levodopa Therapy on inflations risked did not interact with Agonist State,  $F(1,37)=1.78, p=0.19$ , nor with ICD Status,  $F(1,37)=0.03, p=0.86$ . None of the higher order interactions involving Levodopa Therapy were statistically significant. Notably, the ratio of patients on DAA monotherapy versus DAA plus levodopa therapy was similar between PD-ICD (7:15) and PD-C (8:11) groups, ( $\chi^2=0.03, df=1, p=0.87$ ).