The long-term outcome of impulsive compulsive behaviours in Parkinson's disease.

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INTRODUCTION

Impulsive compulsive behaviours (ICBs) such as dopamine dysregulation syndrome, pathological gambling, compulsive sexual behaviour, punding, compulsive shopping and binge eating are recognised complications of dopaminergic treatment that affect at least 1 in 7 patients with Parkinson's disease (PD).[1] Only a few studies provide long-term data on ICBs although any firm conclusions are limited by restricted follow up periods. We present long-term longitudinal data on 46 PD patients with ICBs with follow up for a mean period of 8.2 years.

METHODS

Patients with PD and ICBs who participated in previous research studies from 2007 to 2012 (V1) were invited for re-assessment (V2). Participants underwent a clinical interview and assessment with questionnaires and scales (detailed in supplementary materials). The diagnosis of ICBs was based on screening questionnaires and confirmed with a structured interview. The study received ethics approval. Data was analysed in SPSS 22. All variables were tested for normality and statistical tests chosen accordingly. A p value < 0.05 was considered significant. Bonferroni correction was applied for comparison between visits and significance was considered to have been reached when p < 0.025.

RESULTS

Of the 90 original participants, 46 were included. 8 declined to participate, 5 were lost to follow up and 31 had died (see supplementary figure 1). No cases of suicide or traumatic fatality were reported. Participants were followed up for 8.2 years (± 2.6). Three patients had a bi-allelic PARKIN mutation. See table 1 for demographic and clinical details at each visit and supplementary table 1 for results of the scales/questionnaires used at V2.

Initial treatment of ICBs consisted of cessation of oral/transcutaneous dopamine agonists (DA) in 29 patients, reduction of DA dose in 13 and reduction of levodopa in 4. Seven patients (16.6%) developed dopamine agonist withdrawal syndrome (DAWS). Of the 46 patients, 19 (41.3%) improved completely and were asymptomatic at V2, 26 (56.5%) improved partially and 1 (2.2%) had no change of the addictive behaviour. No patients experienced worsening of ICBs over time. Five patients re-started DA. Details on the outcome of ICBs according to treatment can be seen in supplementary figure 1.

Participants were divided into two groups based on the presence of ICBs at V2 and compared to identify any factors associated with long-term remission (see supplementary table 2). Patients with active ICBs at V2 scored higher in the QUIP-RS, HADS total, HADS depression, UPDRS part I and Hoehn & Yahr scale. To assess if different ICBs were associated with different dopaminergic drugs, patients with DDS and/or punding (which are more associated with l-dopa use) were compared to patients with other ICBs such as pathological gambling (which are more associated with DA use). No differences were found (see supplementary tables 3-5).

	Visit 1 (V1)	Visit 2 (V2)	p value
Age (years)	54.76 (± 9.7; 34 - 72)	61.7 (±10.2; 37 – 81)	**<0.001***
ICBs	46 (100%)	27 (58.7%)	**<0.001$^\lambda$**
Multiple ICBs	27 (58.7%) N = 46	16 (59.2%) N = 27	0.754$^\lambda$
Types of ICBs	DDS = 6	DDS = 3	0.508$^\lambda$
	CSB = 23	CSB = 13	0.052$^\lambda$
	PG = 13	PG = 5	**0.008$^\lambda$**
	CS = 17	CS = 5	**0.008$^\lambda$**
	CE = 11	CE = 14	0.629$^\lambda$
	Punding = 23	Punding = 18	0.359$^\lambda$
UPDRS III	16.22 (± 7.87; 4 - 37)	34.65 (± 11.01; 12 - 61)	**<0.001***
Dyskinesias	29 (63%)	38 (82.6%)	**0.022$^\lambda$**
Cognitive impairment	2 (4.3%)	15 (32.6%)	**0.001$^\lambda$**
Depression	14 (30.4%)	11 (23.9%)	0.629$^\lambda$
Anxiety	8 (17.4%)	15 (32.6%)	0.118$^\lambda$
Hallucinations	10 (21.7%)	12 (26.1%)	0.754$^\lambda$
Use of levodopa	41 (89.1%)	44 (95.6%)	0.375$^\lambda$
Use of DA	42 (91.3%)	18 (39.1%)	**<0.001$^\lambda$**
DA type	Pramipexole = 27	Pramipexole = 8	
	Ropinirole = 12	Ropinirole = 3	
	Rotigotine = 1	Rotigotine = 7	
	Bromocriptine = 1		
	Cabergoline = 1		
Use of MAOi	8 (17.4%)	28 (60.9%)	**<0.001$^\lambda$**
Use of Amantadine	16 (34.8%)	37 (80.4%)	**<0.001$^\lambda$**
Levodopa dose	713.75 (± 487.33; 150 – 2400) N = 41	1021.91 (± 437.5; 200 – 2222) N = 44	**0.001$^\varphi$**
DA LEDD	255.6 (± 113; 52 – 600) N = 42	153.44 (± 86.9; 40 – 360) N = 18	**0.003$^\varphi$**
Total LEDD	979.65 (±542.8; 300 – 2710)	1296.60 (± 457.7; 257 – 2528)	**<0.001**
Infusion therapies	Apomorphine – 1 (2.1%)	Apomorphine: 6.5% (N=3) Duodopa: 2.17% (N=1)	
DBS	0	11 (23.9%) STN = 10; GPi = 1	

Differences between visits. ICBs – impulsive compulsive behaviours; DDS – dopamine dysregulation syndrome; CSB – compulsive sexual behaviour; PG – pathological gambling; CS – compulsive shopping; CE – compulsive eating; UPDRS – Unified Parkinson's Disease; DA – oral or transcutaneous dopamine agonists; MAOi – monoamine oxidase inhibitors; LEDD – levodopa equivalent daily dose as described by Tomlinson et al, 2010; DBS – deep brain stimulation; STN – subthalamic nucleus; GPi – globus pallidus internus. Rating Scale. Results are expressed in total values with proportion, or mean values with standard deviation and range. Significant results after Bonferroni correction in bold. *paired t-test; $^\varphi$Wilcoxon matched pairs; $^\lambda$ McNemar's test.

DISCUSSION

Despite using different methodologies, all previous follow up studies have reported improvement of ICBs after cessation/reduction of DA.[2-4] Reduction of dopaminergic medication also led to improvement in all but one of our patients. However, we found a lower remission rate (41.3%) than previously reported, despite achieving similar reduction in DA use to other reported studies. Continued use of DA as a consequence of DAWS, relapses of behavioural addictions following the necessary concomitant increase in l-dopa dosage, and the inclusion of more severe cases from a tertiary centre are possible explanations for the lower remission rate.

Compared to V1, fewer patients were using DA and more were using MAOi and amantadine at V2. The increase in amantadine use is probably an attempt to control levodopa induced dyskinesias, a common comorbidity of ICBs.[1] Although both these classes of drugs appear to be safer than DA in patients with ICBs, contradictory data has been published on the propensity of amantadine to induce ICBs and a few case reports of ICBs in patients receiving MAOi have also been published.[1] More patients were also taking rotigotine and apomorphine at V2. Some studies have reported a lower proclivity of both these drugs to induce ICBs.[1]

The proportion of patients having multiple ICBs remained stable at V2, in agreement with a prospective two year study.[5] However, we have found a higher prevalence of multiple ICBs than previously reported.[1] The presence of ICBs was associated with depression and lower quality of life.[1] ICBs at V2 were also associated with higher UPDRS part I scores, and more advanced disease. The latter finding is in contradiction to published data showing that ICBs are not associated with disease severity.[5] Patients with more advanced disease require higher doses of dopaminergic treatment and may, therefore, be at increased risk of recurrence of ICBs. A third of patients exhibited cognitive impairment at V2, supporting previous work suggesting ICBs are not a risk factor for PD dementia.[5]

A lower proportion of patients were using neuroleptic drugs at V2 compared with the findings of Sohtaoglu and colleagues.[3] In their study, neuroleptics were used routinely if patients did not improve after initial treatment with reduction of DA. DBS appears to be associated with low risk of ICBs, probably as a consequence of the reduction in dopaminergic treatment that usually follows the procedure. In our study, seven patients were still symptomatic after DBS, but none experienced worsening of ICBs.

Potential limitations of this study are that only half of the patients were available for re-assessment and there was no control group. The mortality rate found here is similar to what has been described among PD patients with similar age at disease onset. Diagnostic accuracy can also be a problem as patients and relatives commonly under-report ICBs.[1] We believe the use of interviews aided by questionnaires at both visits contributed to accurate detections of ICBs.

CONCLUSION

In the longest follow up study of ICBs in PD to date, we have found a lower rate of remission of ICBs than reported in previous studies with shorter follow up periods. The most used treatment strategy was cessation of DA, but 40% of the patients were still receiving these drugs at follow up. Even when reduction or discontinuation of DA was possible it did not guarantee long-term remission.

Competing interests
The authors declare no competing interests regarding this manuscript.

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