

Assessment of therapeutic strategies for management of impulse control disorder in Parkinson's disease

Evaluación de las estrategias terapéuticas en trastornos del control de impulsos en enfermedad de Parkinson

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ABSTRACT

Background: Impulse control disorders (ICD) occur frequently in individuals with Parkinson's disease. So far, prevention is the best treatment. Several strategies for its treatment have been suggested, but their frequency of use and benefit have scarcely been explored. **Objective:** To investigate which strategy is the most commonly used in a real-life setting and its rate of response. **Methods:** A longitudinal study was conducted. At the baseline evaluation, data on current treatment and ICD status according to QUIP-RS were collected. The treatment strategies were categorized as "no-change", dopamine agonist (DA) dose lowering, DA removal, DA switch or add-on therapy. At the six-month follow-up visit, the same tools were applied. **Results:** A total of 132 individuals (58.3% men) were included; 18.2% had at least one ICD at baseline. The therapeutic strategy most used in the ICD group was no-change (37.5%), followed by DA removal (16.7%), DA switch (12.5%) and DA lowering (8.3%). Unexpectedly, in 20.8% of the ICD subjects the DA dose was increased. Overall, nearly 80% of the subjects showed remission of their ICD at follow-up. **Conclusions:** Regardless of the therapy used, most of the subjects presented remission of their ICD at follow-up. Further research with a longer follow-up in a larger sample, with assessment of decision-making processes, is required in order to better understand the efficacy of strategies for ICD treatment.

Keywords: Parkinson Disease; Disruptive, Impulse Control, and Conduct Disorders; Treatment Outcome.

RESUMEN

Antecedentes: Los trastornos del control de impulsos (TCI) son frecuentes en personas con enfermedad de Parkinson. A la fecha, la prevención es el mejor tratamiento. Existen varias estrategias sugeridas para su tratamiento, pero su frecuencia de uso y beneficio ha sido escasamente explorada. **Objetivo:** Investigar qué estrategia es la más utilizada en un entorno de la vida real y su tasa de respuesta. **Métodos:** Se realizó un estudio longitudinal. En la evaluación inicial, se recopiló el tratamiento actual y el estado del TCI de acuerdo con el QUIP-RS. La estrategia de tratamiento se clasificó como "sin cambios", reducción de la dosis de agonista de la dopamina (AD), eliminación de AD, cambio de AD o terapia complementaria. En la visita de seguimiento a los 6 meses, se aplicaron las mismas herramientas. **Resultados:** Se incluyeron un total de 132 (58.3% hombres) personas. El 18.2% tenía al menos un TCI al inicio del estudio. La estrategia terapéutica más utilizada en el grupo de TCI fue sin cambios (37.5%), seguida de eliminación de DA (16.7%), cambio de AD (12.5%) y reducción de DA (8.3%). En el 20.8% de los sujetos con TCI se aumentó la dosis de AD. Casi el 80% de los sujetos tuvieron una remisión del TCI al seguimiento. **Conclusiones:** Independientemente de la terapia utilizada, la mayoría de los sujetos tuvieron una remisión del TCI. Se requiere más investigación con un seguimiento y una muestra mayor para evaluar el proceso de toma de decisiones para comprender mejor la eficacia de las estrategias.

Palabras clave: Enfermedad de Parkinson; Trastornos Disruptivos, del Control de Impulso y de la Conducta; Resultado del Tratamiento.








INTRODUCTION

Parkinson's disease (PD) is a common adult-onset neurodegenerative disease characterized by relatively selective loss of

neuronal subtypes, notably those of the nigrostriatal dopaminergic pathway¹. PD is characterized by motor symptomatology, including bradykinesia, rigidity, postural instability and resting tremor. On the other hand, PD is also accompanied by

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Conflict of interest: There is no conflict of interest to declare.

Authors' contributions: FH, YRS, SLA, CST: data acquisition; MRV, FH, YRS: study conception and design; OEZ, ACA: data analysis and interpretation; MRV, YRS, OEZ, ACA: drafting, reviewing and final approval of the manuscript.

Received on October 26, 2020; Received in its final form on December 22, 2020; Accepted on January 13, 2021.

a myriad of nonmotor manifestations, including cognitive and neuropsychiatric disorders². Impulse control disorders (ICDs) are defined as a group of disorders characterized by behavioral disinhibition including pathological gambling, compulsive shopping, hypersexuality and binge eating. Other related disorders, such as dopaminergic dysregulation syndrome (DDS), punding and hobbyism are also considered to form of the clinical spectrum^{3,4}.

ICDs have been reported to occur in 3.5% to 42.8% of individuals with PD, depending on the study population and methodology; moreover, up to 29% of the patients suffer more than one type of ICD⁵⁻⁸.

ICDs in PD have been associated with dopaminergic therapy, younger age at PD onset, smoking history, personal or family history of alcohol abuse, greater novelty-seeking behavior, impulsivity and depressed mood⁹. In addition, genetic factors, such as DOPA decarboxylase gene polymorphisms, may also play a role in the risk of ICD development¹⁰.

These disorders usually occur without the patient being aware of the symptoms¹¹. However, ICDs can lead to severe consequences, including major financial loss, bankruptcy, disrupted social relationships, divorce, institutionalization and legal problems, with a great impact on the quality of life (QoL) of these patients and increased caregiver distress¹²⁻¹⁴.

So far, the best treatment is preemption and prevention. The strategies that have been suggested include switching the dopamine agonist (DA), tapering down or discontinuing the DA, use of atypical antipsychotics such as quetiapine or clozapine, cognitive behavioral therapy and deep brain stimulation^{15,16}. Currently, there is no consensus or guidelines on which therapeutic strategy is more effective. Evidence on the frequency of use and efficacy of each strategy is scarce.

The objective of this study was to determine which therapeutic strategy is the most frequently used for management of ICDs in a real-life PD sample and to assess its rate of response.

METHODS

A longitudinal study among consecutive patients with a clinical diagnosis of PD in accordance with the Movement Disorder Society clinical diagnostic criteria was conducted¹⁷. These patients attended the outpatient clinic of the Movement Disorder Clinic of the National Institute of Neurology and Neurosurgery between September 2014 and August 2019. Only patients who had a baseline visit and a follow-up visit at 6 ± 1 months were included.

Demographic data including age and sex were collected. The clinical data collected included disease duration, antiparkinsonian drug use and daily dose of levodopa equivalents (LEDD)¹⁸.

At each visit, the following clinical tools were applied by a neurologist with expertise in movement disorders.

The Movement Disorder Society Unified Parkinson's Disease Scale (MDS-UPDRS), which comprises four parts, was used. Part I evaluates non-motor experiences of daily life (0-52 points); part II

assesses motor experiences of daily life (0-52 points); part III comprises a motor examination (0-108 points); and part IV assesses motor complications (0-24 points)¹⁹.

The Hoehn and Yahr scale was used to classify subjects with PD according to the severity of their symptoms²⁰. Subjects were classified as presenting mild (stages 1 and 2), moderate (stage 3) or severe disease (stages 4 and 5).

Non-motor symptoms were assessed using the Non-motor Symptoms Scale (NMSS). The NMSS has 30 items divided into nine domains and allows non-motor symptomatology to be graded through inclusion of frequency and severity. The domains include cardiovascular, sleep/fatigue, mood/cognition, perception/hallucinations, attention/memory, gastrointestinal, urinary, sexual and miscellaneous. For each item, a severity rating (from 0 to 3) and a frequency rating (1 to 4) are obtained; these two variables are multiplied together to obtain the total value²¹.

Disease-related quality of life was assessed using the PD Quality of Life Questionnaire (PDQ-8). The PDQ-8 is a disease-specific instrument that assesses eight aspects of health-related quality of life. The domains evaluated are mobility, activities of daily living, emotional wellbeing, stigma, social support, cognition, communication and bodily discomfort. Each item is scored on a Likert-type scale and the total score is transformed into a simplified index (range from 0 to 100) that indicates the degree of overall condition in relation to the patient's quality of life. Values closer to zero indicate better quality of life (PDQ8-SI)²².

Lastly, the presence of ICDs was assessed using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-RS). The QUIP-RS is composed of four main questions (relating to frequent thoughts, desires and behaviors associated with impulse control disorder), each applied to the main symptoms of impulse control disorder (gambling, excessive shopping, hypersexuality and compulsive eating) and related disorders (DDS, punding and hobbyism). A five-point Likert scale (score of 0-4 for each question) is used to measure the frequency of behaviors that have occurred in the last four weeks. The total score ranges from 0 to 112. The following cutoff values for each symptom were used: gambling ≥ 6, compulsive shopping ≥ 8, hypersexuality ≥ 8, binge eating ≥ 7 and hobbies/punding ≥ 7²³.

For the purposes of the present study, the subjects were classified according to the presence of ICD (non-ICD-PD or ICD-PD).

The therapeutic strategy undertaken in the ICD-PD group was recorded and classified as follows. Subjects who remained under the same drug and dose were deemed to be "no-change". Changes to the dopamine agonist treatment were classified as DA dose lowering or as DA removal. DA switch was defined as replacing an immediate-release DA for an extended-release formulation or changing from an oral to a transdermal formulation. Use of a new drug, such as an antipsychotic or amantadine, was considered to be add-on therapy. Use of non-pharmacological

treatment, including cognitive behavioral therapy and deep brain stimulation, was also recorded.

At the follow-up visit, the same clinical tools were applied by the same rater. The success rate for each strategy was defined as the percentage of subjects with ICD at baseline who did not have ICD at the follow-up visit.

This study was approved by the local ethics committee. Signed informed consent was obtained from all the participants.

Statistical analysis

The Shapiro-Wilk test was used to assess normality. Quantitative variables were compared between groups using Student's t test or the Mann-Whitney U test, as needed. Qualitative variables were compared between groups using the chi-square test.

Quantitative variables were compared between the baseline and follow-up visits using a paired t test or the Wilcoxon test, as needed. The McNemar test was used for comparison of qualitative variables between visits. P-values < 0.05 were considered statistically significant. The statistical analyses were performed using SPSS, v.17 (SPSS Inc., Chicago, IL, USA.)

RESULTS

Baseline visit

A total of 55 women (41.7%) and 77 men (58.3%) were included. The mean age at the baseline visit was 61.9 ± 11.9 years. The mean disease duration was 7.4 ± 5.7 years.

The mean total QUIP-RS score at baseline was 4.5 ± 8.3 . A total of 108 subjects (81.8%) did not have ICD, while 24 (18.2%) had at least one ICD. All subjects with ICD were medicated with a DA (six on rotigotine and the remainder on immediate-release pramipexole).

Table 1 compares the main demographic and clinical variables between groups. In summary, no statistically significant differences were found regarding sex and age at onset. Subjects in the ICD-PD group had higher DA-LEDD, total LEDD and MDS-UPDRS I, II and IV, in comparison with the non-ICD-PD group. Also, the total NMSS score was higher in the ICD-PD group. After analyzing individual NMSS domains, only the perceptual problems/hallucinations domain was found to be higher in the ICD-PD group (2.3 ± 4.6 vs 0.5 ± 1.6 ; $p = 0.034$). Subjects in the ICD-PD group had worse quality of life, compared with the non-ICD patients.

The ICD-PD group had a median of one ICD (range 1-3). There were 15 subjects (62.5%) with only one ICD, while 37.5% had multiple ICDs (8.3% had at least three different ICDs).

Regarding individual ICDs, compulsive eating was found in 45.8%, hobbyism in 45.8%, punning in 25%, compulsive shopping in 8.3% and hypersexuality in 4.2%. Pathological gambling was not found in any subject.

The therapeutic strategy most used in the ICD-PD group was no-change (37.5%), followed by DA removal (16.7%), DA switch (12.5%) and DA lowering (8.3%). Unexpectedly, in 20.8% of the ICD-PD subjects, the DA dose was increased. Antipsychotics, cognitive behavioral therapy and deep brain stimulation strategies were not used in any subject.

Follow-up visit

At the follow-up visit, 79.2% of the subjects in the ICD-PD groups showed remission of the ICD, regardless of the strategy used. Consequently, a decrease in the mean total QUIP-RS score in the ICD-PD group was found (18 ± 11 vs 4.2 ± 7.2 ; $p < 0.001$). Conversely, 7.4% of the subjects initially in the non-ICD-PD patients were found to have developed an ICD at the

Table 1. Comparison of main variables between subjects in the non-ICD-PD and ICD-PD groups at baseline.

	Non-ICD-PD n = 108	ICD-PD n = 24	p
Age (years)	62.8 ± 11.9	57.8 ± 11.1	0.06
Male (%)	66 (61.1%)	11 (45.8%)	0.17
DA-LEDD (mg)	152.6 ± 152.4	237.9 ± 143.9	0.014
Total LEDD (mg)	167.4 ± 162.5	290 ± 174.3	0.003
MDS-UPDRS	49.1 ± 20.1	64.8 ± 28.7	0.008
Part I	8.5 ± 5.5	11.9 ± 5.5	0.005
Part II	11.7 ± 8	18.3 ± 10.7	0.003
Part III	27.8 ± 12.4	31.7 ± 15.5	0.31
Part IV	1.1 ± 2.4	2.8 ± 3.4	0.001
QUIP-RS	1.44 ± 2.7	17.96 ± 11.01	<0.001
NMSS	41.84 ± 39.1	55.5 ± 41.7	0.03
PDQ8-SI	21.55 ± 18.9	36.58 ± 24.7	0.001

DA: dopamine agonist; LEDD: levodopa equivalent daily dose; MDS-UPDRS: Movement Disorder Society Unified Parkinson Disease Rating Scale; QUIP-RS: Questionnaire for Impulsive-Compulsive Disorders Rating Scale; NMSS: Non-Motor Symptoms Scale; PDQ8-SI: Parkinson's Disease Questionnaire Summary Index; ICD: impulse control disorder; PD: Parkinson's disease.

follow-up. No difference in MDS-UPDRS III was found at the follow-up, in comparison with the baseline score.

No-change was the most frequent and the most effective strategy with a remission rate of 100%, followed by discontinuing the DA with an effectiveness of 75%. Increasing the DA dose had a success rate of 60%, which was higher than the

rate through lowering DA strategy and similar to switching DA. Table 2 summarizes the therapeutic strategies and their outcomes, and the changes to MDS-UPDRS III and QUIP-RS scores. Overall, only the no-change strategy resulted in a statistically significant improvement in MDS-UPDRS III at follow-up (mean difference of 4.5; 95% CI 3.03-23.6).

Table 2. Therapeutic strategies, MDS-UPDRS part III and QUIP-RS score among subjects with ICD-PD.

Therapeutic strategy	N	Subjects with ICD remission	Subject with ICD	MDS-UPDRS part III			QUIP-RS score		
				Baseline visit	Follow-up visit	p	Baseline visit	Follow-up visit	p
ICD-PD	24	19 (79.2%)	5 (20.8%)	31.7 ± 15.5	28 ± 12.8	0.281	18 ± 11	4.2 ± 7.2	<0.001
No change	9 (37.5%)	9 (100%)	0	24.1 ± 7.6	24.3 ± 7.1	0.735	14.4 ± 13.1	1.1 ± 2.1	0.01
DA discontinuation	4 (16.7%)	3 (75%)	1 (25%)	43 ± 8.1	32.5 ± 14.4	0.109	15.5 ± 8.6	2.3 ± 4.5	0.07
DA switch	3 (12.5%)	2 (66.7%)	1 (33.3%)	33.3 ± 26.4	32.3 ± 28	0.276	19.7 ± 5.7	4 ± 9.7	0.11
DA lowering	2 (8.3%)	1 (50%)	1 (50%)	35 ± 4.2	27 ± 5.6	0.180	25.5 ± 7.8	11.5 ± 7.8	0.18
DA increase	5 (20.8%)	3 (60%)	2 (40%)	25 ± 5.7	26 ± 13	0.686	24.2 ± 11.3	9.4 ± 11.9	0.08
DA add-on	1 (4.2%)	1 (100%)	0	77	41	0.317	8	0	-

DA: dopamine agonist; MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale; QUIP-RS: Questionnaire for Impulsive-Compulsive Disorders Rating Scale; ICD: impulse control disorder; PD: Parkinson's disease.

DISCUSSION

The prevalence of ICD and related disorders in Mexican PD subjects has been reported to be 25.6%²⁴; in this study, the prevalence was lower, at 18.2%. Regarding risk factors for ICD, DA-LEDD and the total LEDD were higher in the ICD-PD group. On the other hand, our study did not find any difference between the groups regarding age or sex. In the case of age, a trend was present but did not reach statistical significance.

Level I evidence on the management of ICD in PD is still lacking; nevertheless, several strategies have been recommended²⁵. Since it has been reported that DA treatment in PD is associated with 2 to 3.5-fold increased odds of having an ICD⁶, the three main approaches include lowering, switching or discontinuing the DA. In our study sample, DA-centered strategies were used for 37.5% of the ICD-PD subjects; the combined remission rate was 66.7%. Nonetheless, the most frequently used therapeutic strategy among ICD-PD subjects was no-change. Regardless of the number of ICD domains affected or the total QUIP-RS score, all subjects managed with this strategy were free from ICD at the follow-up, with no significant change in MDS-UPDRS III.

In the present study, the most striking finding was that in 20.8% of the subjects with ICD, the DA dose was in fact increased. In three out of the five subjects, the ICD remitted. Unfortunately, this study was not designed to assess the decision-making process. Nonetheless, it can be hypothesized that this strategy might be influenced by a trade-off between ICD severity and possible motor benefit.

Several studies have reported relatively high remission rates ranging from 30% to 48.6%, regardless of the strategy used among the patients^{5,26}. It is worth mentioning that those studies were not designed to identify either the strategy used to treat the ICD or the efficacy of the different approaches. Notwithstanding this, the evidence suggests that regardless of the approach used, a large percentage of PD subjects with ICD would achieve resolution of the disorder at a follow-up visit. In most cases, the decision on the strategy should be individualized. For example, the no-change group in our study had a stable score in MDS-UPDRS III and a relatively low score in QUIP-RS, which could have been the main reason for the decision not to change the pharmacological treatment. In other words, the patient's ON state can be prioritized when the ICD does not represent a great disturbance for the patient or does not affect the daily living activities or quality of life. On the other hand, it is very important to consider that patients may underestimate the presence and severity of ICDs, or the impact on their family and caregivers²⁷.

Few factors associated with ICD remission or persistence, other than DA treatment, have been reported. Better performance in working memory-related tasks at baseline has been associated with remission²⁸, although cognitive changes over time do not differ between patients with and without ICD²⁹. Conversely, younger age and personality traits such as higher levels of anger expression and obsessive-compulsive behaviors have been associated with refractory ICD^{30,31}. These variables may also play a role in the high overall rate of remission of ICD

that is seen in PD. Unfortunately, the small sample size and the lack of formal cognitive and personality trait assessments in our study did not allow further analysis on this matter.

Some limitations regarding our study can be listed. First, as mentioned earlier, the factors that contributed to the decision-making by the neurologist were not assessed. Further investigations to address this issue are needed, including the role of shared decision-making. Another limitation was the relatively low prevalence of the ICDs: even though in our sample the prevalence was higher than in some other reports, each strategy group was formed by only a small number of subjects. Studies with larger samples are needed, to confirm our findings. Also, it has been reported that ICDs tend to have a slower risk evolution pattern as the disease progresses³²; while the disease duration in our study sample was similar to what had previously been seen in other large studies, our findings might not be generalizable to subjects with shorter disease durations.

Lastly, the follow-up included only one additional visit and,

thus, relapse could not be assessed. On this matter, the ICARUS study found that there was relatively stable prevalence of ICDs during its two-year follow-up³³. In our study sample, the incidence was around 7% at six months, so it might be expected that a longer follow-up would result in higher numbers of cases. It should be pointed out that ICD relapse has scarcely been reported. Erga et al.²⁹ reported that their relapse rate was 3.7% (n = 82) over a four-year follow-up; in contrast, the DIGPD study²⁶ reported a relapse rate of 31.7% (n = 85), also after a four-year follow-up.

Therefore, further research with a longer follow-up in a larger sample assessing the factors that neurologists considered in the decision-making process is required, to better understand the efficacy of the strategies in the ICDs treatment.

In conclusion, the most frequent and effective therapeutic strategy used in this longitudinal study of subjects with ICD-PD was not to make any changes; but regardless of the strategy, almost 80% showed remission at a six-month follow-up.

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