

# Electroconvulsive therapy in Parkinson's disease

## A eletroconvulsoterapia na doença de Parkinson

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### ABSTRACT

**Objective:** To analyze the effectiveness of electroconvulsive therapy for the management of depression and/or psychosis refractory to drug therapy in patients with Parkinson disease. **Method:** A retrospective study was carried out including patients treated with electroconvulsive therapy during the period between 2002 and 2013. A review of the literature was performed. **Results:** A total of 27 patients were included. In regards to the neuropsychiatric diagnosis, 14 patients had major depression, 12 patients had both psychosis and depression, and only one patient had isolated psychosis. The mean number of electroconvulsive therapy sessions was  $12 \pm 2.8$ . After electroconvulsive therapy, all patients showed a statistically significant improvement in the Brief Psychiatric Rating scale (reduction of 52% points) and Hamilton Depression Rating Scale (reduction of 50% points) independent of the presence of psychosis, depression or both. **Conclusion:** Electroconvulsive therapy is effective for the treatment of refractory neuropsychiatric symptoms in Parkinson's disease.

**Keywords:** Parkinson's disease, electroconvulsive therapy, psychosis, depression.

### RESUMO

**Objetivo:** Analisar a eficácia da eletroconvulsoterapia para o tratamento da depressão e/ou psicose refratária ao tratamento medicamentoso em pacientes com doença de Parkinson. **Método:** Um estudo retrospectivo foi realizado com pacientes tratados com a eletroconvulsoterapia, durante o período entre 2002 e 2013. Uma revisão da literatura foi realizada. **Resultados:** Um total de 27 pacientes foram incluídos. Em relação ao diagnóstico neuropsiquiátrico, 14 pacientes tinham depressão maior, 12 pacientes tiveram tanto psicose e depressão, e apenas um paciente tinha isolado psicose. O número médio de sessões de eletroconvulsoterapia foi de  $12 \pm 2.8$ . Após a eletroconvulsoterapia, todos os pacientes apresentaram uma melhora estatisticamente significativa no Brief Psychiatric Rating Scale (redução de 52% de pontos) e Hamilton Depression Rating Scale (redução de 50% de pontos), independente da presença de psicose, depressão ou ambos. **Conclusão:** Eletroconvulsoterapia é eficaz para o tratamento de sintomas neuropsiquiátricos refratários na doença de Parkinson.

**Palavras-chave:** doença de Parkinson, eletroconvulsoterapia, psicose, depressão.

Parkinson's disease (PD) is characterized by a wide spectrum of motor and non-motor features; the latter include a high prevalence of neuropsychiatric symptoms<sup>1</sup>. Depression and psychosis are among the most frequent neuropsychiatric symptoms in PD<sup>2,3</sup>. Depression and psychosis have been associated with poor health-related quality-of-life and disability<sup>4,5,6</sup>. Psychopharmacotherapy is currently considered the first-line of treatment for depression, as well as for psychosis in patients with PD. A recent meta-analysis on treatment for depression reported a moderate, but non-significant, pooled effect for antidepressants over placebo<sup>7</sup>. The rate of depression remission in PD is 37% to 44%. Regarding psychosis, response rates to antipsychotics have

been reported to be complete in 33% and partial in another 33% of the cases<sup>9,10</sup>.

In refractory cases, the use of electroconvulsive therapy (ECT) has been proved to have beneficial effects on both, neuropsychiatric symptoms and motor symptoms of patients with PD<sup>11,12</sup>. The majority of these studies are uncontrolled prospective or retrospective studies, or case reports. Moreover, the stigma surrounding ECT has may also account for a reduced use of it in the treatment of neuropsychiatric symptoms in subjects with PD.

The objective of the present study is to analyze the effectiveness of electroconvulsive therapy for the management of depression and/or psychosis refractory to drug therapy in

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a relatively large sample of patients with Parkinson disease seen at a tertiary referral center from Mexico.

## METHOD

A retrospective study was carried out. Patients diagnosed with PD according to the clinical criteria of the Brain Bank Society who were treated with electroconvulsive therapy between the years 2002 and 2013 were included. Demographic variables collected included gender, age at the time of ECT, years of education and handedness. Clinical variables included age at motor onset, disease duration, motor phenotype, antiparkinsonian treatment and dosage, presence of motor complications and disease severity in terms of Hoehn and Yahr (HY) stage. The use of antidepressive, anxiolytic or antipsychotic drugs was also recorded. Levodopa equivalent daily dose (LEDD) and dopamine agonist levodopa equivalent daily dose were calculated (DA-LEDD)<sup>13</sup>. Data for LEDD and DA-LEDD calculation was obtained at the time of admission and at the time of discharge.

The following data were collected from the clinical charts: Indication for ECT based on the DSM-IV criteria for depressive disorder or the National Institutes of Health (NIH)-National Institute of Neurological Diseases and Stroke (NINDS)/National Institute of Mental Health (NIMH) diagnostic criteria for psychosis in PD<sup>14</sup>. Patients were classified according to the presence of depression, psychosis or both (independently of the fulfillment of the psychotic features specifier for depression). In accordance to the hospital protocol, each patient is selected for ECT treatment by means of clinical agreement of at least two clinical neuropsychiatrists. In patients with depression, a failure in two or more antidepressant trials, taking into account correct doses and time of administration, must be documented before ECT. In patients with psychosis, a failure of two or more antipsychotics (including both clozapine and quetiapine) must be documented before the indication of ECT. Motor evaluation was assessed using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III). Complications of antiparkinsonian therapy were assessed using the UPDRS part IV. Neuropsychiatric symptoms were assessed using the Spanish versions of the Brief Psychiatric Rating Scale (BPRS) for psychotic symptoms and the Hamilton Rating Scale for Depression (HDRS) for depressive symptoms. All of these assessment tools were administered at admission (pre-ECT) and at discharge (post-ECT).

ECT procedure was performed according to the half-age strategy<sup>15</sup>. Sessions were performed twice or three times per week. All patients were induced with thiopental (dose range of 0.5 to 2 mg/kg) and paralyzed with suxamethonium (1 mg/kg). ECT was performed using a Thymatron® System DGx apparatus (Somatics, IL, USA). The ECT course was terminated when the attending psychiatrist considered that the symptoms had clinically remitted.

After reviewing each patient history, patients with neuropsychiatric symptoms attributable to other conditions were excluded. Patients with incomplete or missing data were also excluded.

In all cases the patient received the best medical treatment and consideration of each specialist individually. Written informed consent for ECT was obtained from each patient or legal guardian before the initial ECT session. Due to the retrospective nature of the study, all data was de-identified and a waiver of informed consent was granted by the ethics committee. The study was approved by both the local investigation committee and by the ethics committee.

Additionally, a comprehensive review of the literature published in PubMed in the last seventeen years was conducted; search terms included "Parkinson's disease", "electroconvulsive therapy", "depression", "psychosis" and "neuropsychiatric symptoms".

## Statistical analysis

Demographic data were reported in terms of percentage, mean and standard deviation. Nominal variables were compared using McNemar test. Differences in total BPRS, total HDRS, and GAF scores and Hoehn and Yahr staging between before and after ECT were analyzed using a paired t test. When data were ordinal or did not fit normal distribution, non-parametric statistics were used. A  $p < 0.05$  was accepted as statistically significant.

## RESULTS

During the 2002-2013 period, 29 patients with PD were admitted to the neuropsychiatry unit for ECT. One patient was excluded due to incomplete data, and a second patient was excluded after being diagnosed with atypical parkinsonism during the follow-up. A total of 27 patients (20 males and seven females) were included in the final analysis. Mean years of schooling were  $8.8 \pm 4.6$ . The mean age of the sample at the time of admission was  $58.9 \pm 13.8$  years. Disease duration was  $104.6 \pm 42.5$  months (range 33 to 202 months). In regards to motor phenotype, 51.9% ( $n = 14$ ) had a tremor-dominant disease, 37% ( $n = 10$ ) had a rigid-bradykinetic predominance and only 11.1% ( $n = 3$ ) had a postural instability gait disorder. All the patients had a right handedness and 51.9% had a right motor asymmetry.

In regards to the neuropsychiatric diagnosis, 14 patients had major depression (51.9%), 12 patients had both psychosis and depression (44.4%), and only one patient had isolated psychosis (3.7%). All patients with psychosis had visual hallucinations; additionally five patients had delusions (38.4%), two patients had false sense of presence (15.4%) and only one patient had auditory hallucinations (7.7%).

All of the patients with PD and psychosis were on an antipsychotic. Six patients were on clozapine (range dose 50 to 150 mg/d) and six on quetiapine (range dose 50 to 100 mg/d).

Mean duration of psychosis at the time of ECT was  $27.7 \pm 30.5$  months (range of 6 to 96 months).

On the other hand, all patients with PD and depression were on an antidepressant. Eleven patients were on tricyclic (amitriptyline in all cases) and 15 on a selective serotonin reuptake inhibitor (seven were on citalopram, five on sertraline, and three on fluoxetine). Mean duration of depression at the time of ECT was  $57.4 \pm 41.3$  months (range of 6 to 120 months).

The comparison of antiparkinsonian treatment before and after the ECT course is shown in Table 1. No differences were found in the levodopa daily dose, DA-LEDD or LEDD reduction between patients with depression alone or depression and psychosis. Regardless of the response to ECT, antidepressant or antipsychotic were not discontinued in any patient.

All but two patients had the electrodes placed in a bilateral frontotemporal manner. The mean number of ECT sessions was  $12 \pm 2.8$  (range of 4, median 12). The mean time between initial and final clinical evaluation was  $2.9 \pm 0.9$  weeks. There were no statistically significant differences between patients with psychosis and depression in comparison with those with depression alone ( $8.4 \pm 3.5$  versus  $9.3 \pm 1.8$ , respectively).

The initial stimulus dose ranged from 35% (176.4 millicoulombs) to 65% (320 millicoulombs) with a median of 50%. The mean final stimulus dose was 50% (range 20% to 35%). The motor seizure lasted between 48 and 63 seconds (median of 55 seconds), and the electroencephalographic seizure lasted between 62 and 80 seconds (median of 71 seconds).

The neuropsychiatric symptoms resolved in all cases. The comparison of the clinical scales scores for the whole sample is shown in Table 2. No statistically significant differences were found in any of the motor and neuropsychiatric scales when patients with psychosis and depression were compared to those with depression alone ( $p > 0.10$  in all cases). Patients with depression and psychosis did show a slighter, but non-significant, improvement in the BPRS score than those with depression alone (reduction of  $10.5 \pm 6.9$  points versus  $7.5 \pm 5.5$  points,  $p = 0.23$ ). No difference was found when comparing the change of the total HDRS score between both groups (reduction of  $11.1 \pm 2.5$  versus  $10.3 \pm 2.3$  points,  $p = 0.41$ , respectively).

After the ECT treatments, the motor symptoms improved as assessed by the UPDRS parts III (mean difference of  $17.6 \pm 10.2$ ,  $p < 0.001$ ) and IV (mean difference of  $4.3 \pm 3.3$ ,  $p < 0.001$ ).

In general, ECT was well tolerated. Eight patients did show disorientation after the procedure, in all cases the confusional state was transient and resolved without any additional treatment.

## DISCUSSION

Depression and psychosis in subjects with Parkinson's disease impair the quality of life. Antidepressants and antipsychotics are considered the first-line of treatment for these neuropsychiatric symptoms. Electroconvulsive therapy should

**Table 1.** Comparison of drug treatment before and after the sessions of electroconvulsive therapy.

	Before ECT	After ECT	p
Use of levodopa	27 (100%)	27 (100%)	--
Levodopa daily dose	$691.7 \pm 300$	$617.6 \pm 283.5$	0.05
Use of dopamine agonist	13 (48.1%)	10 (37%)	0.58
DA-LEDD (mg/d)	$168.8 \pm 152.8$	$126.5 \pm 152.4$	0.17
Use of COMT inhibitor	3 (11.1%)	1 (3.7%)	0.61
Use of MAO inhibitor	4 (14.8%)	1 (3.7%)	0.35
Use of amantadine	2 (7.4%)	0 (0%)	0.49
Use of biperiden	5 (18.5%)	3 (11.1%)	0.70
LEDD (mg/d)	$818.9 \pm 362.9$	$712.6 \pm 355.6$	0.01

ECT: Electroconvulsive therapy; DA-LEDD: Dopamine agonist – levodopa equivalent daily dose; COMT: Catechol-O-methyltransferase; MAO: Monoamine oxidase; LEDD: Levodopa equivalent daily dose.

**Table 2.** Clinical evaluation before and after the sessions of electroconvulsive therapy.

	Before ECT (mean $\pm$ SD)	After ECT (mean $\pm$ SD)	p
UPDRS III (n = 23)	$45.2 \pm 14.1$	$27.6 \pm 11.9$	$< 0.001$
UPDRS IV (n = 23)	$7 \pm 3.1$	$2.7 \pm 1.1$	$< 0.001$
HY (n = 21)	$3.2 \pm 0.6$	$2.1 \pm 0.5$	$< 0.001$
MMSE (n = 27)	$26.5 \pm 3.9$	$26.3 \pm 4.2$	0.79
CGI (n = 27)	$4.7 \pm 0.8$	$2.9 \pm 1$	$< 0.001$
BPRS (n = 27)	$18.4 \pm 8.6$	$9.6 \pm 5.7$	$< 0.001$
HDRS (n = 27)	$21.1 \pm 2.2$	$10.5 \pm 3$	$< 0.001$

ECT: Electroconvulsive therapy; SD: Standard deviation; UPDRS: Unified Parkinson's disease rating scale; HY: Hoehn and Yahr; MMSE: Minimal mental status examination; CGI: Clinical global impression; BPRS: Brief psychiatric rating scale; HDRS: Hamilton depression rating scale.

be considered for those with refractory symptoms or in whom serious side effects from drug therapy have developed<sup>16</sup>.

ECT has been reported as a successful procedure for neuropsychiatric symptoms in patients with Parkinson's disease, including psychosis<sup>11,17</sup>, anxiety<sup>18</sup>, depression<sup>19</sup> and obsessive-compulsive disorder<sup>20</sup>. Most of the currently available literature is comprised of uncontrolled prospective or retrospective studies, case-series, or single case reports. The summary of the published reports is presented in Table 3.

We present a relative large series of 27 patients with PD who underwent ECT for the treatment of refractory psychosis and/or depression.

In our sample, all patients showed a statically significant improvement in the BPRS and HDRS independent of the presence of psychosis, depression or both. The BPRS showed an improvement of 47.8%, while the HDRS had a reduction of 50.2%. Comparison of our results with other studies is difficult due to differences in clinimetric assessments and study design. The improvement in the BPRS is lower than that reported by Ueda et al.<sup>12</sup>; although their sample was low in comparison to the present study.

Dopaminergic replacement treatment has been associated with a higher risk of developing psychosis<sup>21</sup>. Conversely, it has been suggested that dopaminergic treatment, specifically

**Table 3.** Summary of published reports of electroconvulsive therapy for the management of neuropsychiatric symptoms in subjects with Parkinson's disease.

Study	Sample	Neuropsychiatric disorder	Measurements	Findings
Nishioka et al, 2014	4	Psychosis	NPI HAM-D	Improvement of 89.8% in the NPI. Improvement of 81.1% in the HAM-D
Sadananda, et al, 2013	1	Psychosis	PANNS	Improvement of 77.3% in the PANNS
Muhammad et al, 2012	1	Obsessive-compulsive disorder	Clinical impression	Improvement
Usui et al, 2011.	8	Psychosis	SAPS	Improvement of 65.8% in the mean SAPS total
Ducharme et al, 2011.	1	Depression	Clinical impression	Improvement
Ueda et al. 2010.	5	Psychosis	BPRS HAM-D	Improvement of 89.2% in the BPRS Improvement of 83.8% in the HAM-D
Bailine et al. 2008.	1	Psychotic depression	Clinical impression	Improvement
Lance et al, 1998.	1	Depression	Clinical impression	Improvement
Mollentine et al, 1998.	25	Depression and/or psychosis, dementia.	BPRS HAM-D	
Nymeyer et al, 1997.	1	Depression	Clinical impression	Improvement
Factor et al, 1995	2	Depression and/or psychosis	Clinical impression	Improvement
Sandky et al, 1993.	1	Psychotic depression	Clinical impression	Modest improvement
Oh et al, 1992.	11	Depression and/or psychosis	Clinical impression	82% of the patients improved
Zwil et al, 1992	8	Depression and/or psychosis		
Friedman et al, 1992.	5	Depression and/or psychosis	Clinical impression	Improvement
Stern, 1991.	1	Depression	Clinical impression	Improvement
Liberzon et al, 1990.	1	Psychotic depression	Clinical impression	Improvement

NPI: Neuropsychiatric inventory; HAM-D: Hamilton depression rating scale; PANNS: Positive and Negative Syndrome Scale; SAPS: Scale for the Assessment of Positive Symptoms; BPRS: Brief Psychiatric Rating Scale.

pramipexole, might in fact have an antidepressant effect independent of the motor improvement<sup>22</sup>. In our study, the mean LEDD showed a statically significant reduction when comparing the before and after ECT data. The reduction of levodopa daily dose showed a tendency to statistical significance, while the DA-LEDD difference was not significant. This suggests that the combined effect of reducing levodopa and dopamine agonists is responsible for the overall reduction in the LEDD. This reduction in the LEDD could partially explain the improvement in psychosis. Also, the motor improvement seen in the UPDRS after the ECT probably allowed the reduction on the dopaminergic therapy without risking the motor state of the patient. Also, ECT could produce a direct antipsychotic effect by means of dopamine receptors modulation<sup>23</sup>.

ECT has also been proved safe and effective in managing motor symptoms in PD patients including reductions in "off" time<sup>24</sup> and motor fluctuations<sup>25</sup>. Conversely, Pintor et al recently failed to replicate these findings although they did find an improvement on freezing<sup>26</sup>. In our case-series an improvement of approximate 30% in the UPDRS III was found. Moreover, the reduction in the UPDRS IV was around 39%. Nevertheless, we must emphasize that the motor evaluation was carried out in the neuropsychiatry unit, and change in motor function was not considered a priori as an endpoint.

On the other hand, Usui et al reported an improvement in psychosis after ECT, but also in the severity of PD in terms of HY stage<sup>27</sup>. In the present study, a statistically significant improvement in HY stage of one point was found, although the clinical significance of it is not known.

The mechanism of action of ECT is unknown. It has been hypothesized that ECT increases responsiveness to post-synaptic dopamine, upregulates dopamine receptors in the striatum and increases the levels of levodopa by disrupting the blood-brain barrier<sup>28,29</sup>. Additionally, ECT enhances the serotonergic neurotransmission and mesocorticolimbic pathways activation<sup>30</sup>. A study using positron emission tomography in patients with psychotic depression showed that ECT led to a significant increase in the left subgenual anterior cingulate cortex and hippocampal metabolism, which were correlated with reductions in HDRS scores. The reduction in positive symptoms was correlated with an increase in left hippocampal metabolism<sup>31</sup>. These effects may explain the mechanisms underlying the antidepressant and antipsychotic effects of ECT.

The safety and tolerability of the ECT procedure was remarkable. No serious adverse effects were reported. This might be the result of an adequate pre-ECT evaluation highlighting the importance of case selection and interdisciplinary management of the patient with PD.

The study has several limitations. First, the limitations of retrospective analyses must be considered including patient and treatment selection biases, as well as reliance on medical record keeping. Second, all included patients were evaluated using the same neuropsychiatric scales during their "on" state, but the raters differed over the time and they were not blinded. As a consequence rater bias cannot be excluded.

Third, the motor evaluation using the UPDRS was not standardized nor applied by a movement disorder



specialist, thus limiting its value in the present study. Additionally, there was no control group. It should also be noted that the presence of apathy, commonly overlapped with depression, was not assessed. Finally, the long-term efficacy was not explored.

Despite these limitations, we consider that ECT was effective and safe for the acute treatment of refractory psychosis and/or depression in patients with Parkinson's disease. A large, randomized sham-controlled trial of ECT for the treatment of neuropsychiatric symptoms in PD is still needed.

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