Pathological Gambling in Parkinson Disease Is Reduced by Amantadine

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To investigate the possible efficacy of amantadine in the control of pathological gambling (PG) associated with Parkinson disease (PD), 17 PD patients with PG were randomly selected for a double-blind crossover study with amantadine 200mg/day versus placebo and an open follow-up. Assessments included PG-specific scales (Yale-Brown Obsessive-Compulsive Scale for PG, Gambling-Symptom Assessment Scale, South Oaks Gambling Screen) and assessment of expenditures and time spent gambling. Amantadine abolished or reduced PG in all treated patients, as confirmed by scale score and daily expenditure reduction. Amantadine might be useful to treat PG. The effect of amantadine, acting as an antiglutamatergic agent, also opens new insights into the pathogenesis of PG.

Impulse control disorder (ICD) is defined as failure to resist an impulse, or as the drive or temptation to carry out a harmful act. It is considered, along with dopamine dysregulation syndrome (DDS) and repetitive non-goal-oriented behaviors (punding), to be a frequent disorder in Parkinson disease (PD). In PD, typical ICD includes hypersexuality, pathological gambling (PG), compulsive shopping, or compulsive eating; 6 to 7% of PD patients meet criteria for 1 of these disorders. Lifetime prevalence of ICD is 6.1% in all PD patients, and 13.7 to 17.1% in PD patients on dopamine agonists (DA).

Recent studies hypothesize that L-dopa–induced dyskinesias and behavioral alterations observed in DDS and ICD depend on common mechanisms involving alterations of glutamate homeostasis with combined activation of sensitized dopamine and N-methyl-D-aspartate (NMDA) glutamatergic receptors. Imbalance between synaptic and nonsynaptic glutamate might result in failure of prefrontal cortex control.

No treatments are at present validated for ICD or DDS; reduction and withdrawal of DA are considered possible options, but DA withdrawal may induce severe worsening of motor control. Clozapine has been shown in anecdotal reports to reduce hypersexual behaviors, but no evidence supports its use in other ICDs. The antiglutamatergic acamprosate (Ca acetyl-homotaurine) is undergoing phase 2 studies.

Amantadine, an antiglutamatergic drug with NMDA receptor antagonist properties, introduced for the treatment of early PD motor symptoms based on original serendipitous findings and also able to reduce dyskinesias, reduced punding behavior in a PD patient.

In the present study, we aimed to test the ability of amantadine to possibly reduce ICD in PD. We selected PD patients recently affected by PG, as this ICD is frequent, economically disruptive, and quantifiable and has been a source of complex legal actions.

Patients and Methods

Seventeen patients with PD according to UK Brain Bank Criteria, with severe PG identified in the last 10 months that was not decreased by DA reduction or withdrawal or behavioral strategies, were selected from a cohort of 1,096 PD patients regularly followed at our Movement Disorder Clinic.

PG was identified according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (rule of 5 of 9 items) and South Oaks Gambling Scale (SOGS) criteria. Patients affected by manic episodes or bipolar disorder and patients receiving antipsychotics or anticholinergics or previously exposed to amantadine were excluded from the study.

PD symptoms were evaluated with the Unified Parkinson’s Disease Rating Scale, PD stage with the Hoehn/Yahr (H/Y) scale, cognition with the Mini-Mental State Examination,
and behavioral and mental functions with the Neuropsychiatry Inventory.\textsuperscript{16}

The study received approval by our local ethical committee, according to the Declaration of Helsinki and subsequent revisions.\textsuperscript{17} After complete description of the study, all subjects signed written informed consent.

**Study Design**

To assess the effect of amantadine on PG, a 17-week, double-blind, placebo-controlled, crossover open extension study on amantadine treatment was designed, consisting of 4 weeks baseline and 8 weeks amantadine/placebo with 1 week washout and 4 weeks follow-up.

The study design and Consolidated Standards of Reporting Trials (CONSORT) statement checklist are reported as supplementary material (Supplementary Study Design and Supplementary CONSORT Statement, respectively).

PG was quantified by blinded raters with the Gambling-Symptom Assessment Scale (G-SAS)\textsuperscript{18} and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) for PG.\textsuperscript{19} Daily diaries assessed the time spent gambling and gambling cost in each day of the week. Patients’ reports were double-checked with caregivers.

Assessments were performed twice during the baseline (run-in) period of 4 weeks (T1 and T2) and twice during the follow-up period of 4 weeks, where only 12 patients received amantadine (T6, T7). Randomization at the end of the baseline period (T2) assigned amantadine/placebo with a ratio 1:1. During the crossover period, assessments were done at T3 after 2 weeks of treatment (first crossover branch), at the end of the 1-week washout period (T4), and at T5 after 2 weeks of treatment (second crossover branch). Amantadine was administered as an add-on to the current antiparkinsonian medications, consisting of DA in monotherapy (4 patients), L-dopa in monotherapy (4 patients), L-dopa and DA therapy (9 patients), entacapone (7 patients), and rasagiline (all), unmodified throughout the study.

Amantadine tablets were triturated and inserted into polymide capsules; identical capsules containing agar gel were used as placebo.

Amantadine or placebo were administered by a nurse unaware of patients assignments, with a titration schedule of 50mg twice daily (bid) for 2 days and 100mg bid in the following 2 weeks, and was withdrawn in 2 days (50mg bid) during period T4.

All patients had 24-hour access to clinicians to inform about effects of treatments or of withdrawals.

**Statistics**

Baseline characteristics were compared between treatments using analysis of variance for continuous variables and chi-square test analyses for dichotomous or categorical variables.

Differences in the G-SAS and Y-BOCS scores between treatments, at baseline and at follow-up, were tested by mixed models analysis of covariance.\textsuperscript{20} Analyses were adjusted for age, sex, H/Y stage, and disease duration.

**TABLE: Demographics and Clinical Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>13/4</td>
</tr>
<tr>
<td>Age, yr (range)</td>
<td>61.0 ± 1.6 (53-74)</td>
</tr>
<tr>
<td>PD DD, mo (range)</td>
<td>52.4 ± 7.8 (8-106)</td>
</tr>
<tr>
<td>H/Y stage (range)</td>
<td>1.9 ± 0.2 (1-3)</td>
</tr>
<tr>
<td></td>
<td>6 patients H/Y stage 1-1.5; PD DD, 3-14 mo</td>
</tr>
<tr>
<td></td>
<td>5 patients H/Y stage 2-2.5; PD DD, 39-52 mo</td>
</tr>
<tr>
<td></td>
<td>6 patients H/Y stage 3; PD DD, 48-106 mo</td>
</tr>
<tr>
<td>L-dopa dose, mg (range)</td>
<td>223.5 ± 49.2 (0-500)</td>
</tr>
<tr>
<td>DA Eq dose, mg (range)</td>
<td>1.2 ± 0.4 (0-3)</td>
</tr>
<tr>
<td>Duration of L-dopa treatment, mo (range)</td>
<td>18.7 ± 5.7 (22–81)</td>
</tr>
<tr>
<td>Duration of DA treatment, mo (range)</td>
<td>47.4 ± 7.3 (8–92)</td>
</tr>
<tr>
<td>Duration of PG, mo (range)</td>
<td>7.1 ± 0.4 (4-9)</td>
</tr>
<tr>
<td>Daily expenditures, % of salary</td>
<td>B 2.0 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>A-d4 0.01 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>A-d14 0.01 ± 0.1</td>
</tr>
<tr>
<td>SOGS</td>
<td>15.1 ± 2.3</td>
</tr>
<tr>
<td>SAS</td>
<td>B 30.9 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>P 31.2 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>A 21.6 ± 0.9</td>
</tr>
<tr>
<td>Y-BOCS</td>
<td>B 28.0 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>P 28.0 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>A 17.3 ± 0.7</td>
</tr>
<tr>
<td>UPDRS-IV items 32-33 (complications of therapy)\textsuperscript{a}</td>
<td>B 4.2 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>P 4.1 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>A 2.2 ± 0.4</td>
</tr>
</tbody>
</table>

\textsuperscript{a}UPDRS-IV items 32-33 report dyskinesias, as amantadine is known to reduce dyskinesias. Only 4 of 6 patients in H/Y stage 3 had dyskinesias.

M = male; F = female; PD = Parkinson disease; DD = disease duration; H/Y = Hoehn/Yahr; DA = dopamine agonist; Eq = equivalent (1mg pramipexole equals 4mg ropinirole); PG = pathological gambling; B = before treatment; A-d4 = 4 days after amantadine treatment introduction; A-d14 = 14 days after amantadine treatment introduction; SOGS = South Oaks Gambling Scale; SAS = Symptom Assessment Scale; P = placebo; A = amantadine; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; UPDRS-IV = Unified Parkinson’s Disease Rating Scale IV.
For dropped-out patients, the worst score reached at the G-SAS and Y-BOCS during the run-in phase was considered as the score at the end of the study (intention to treat analysis).

Order of drug administration was the variable added in the mixed model to evaluate potential carryover effects.

The power of the study was >0.90 (post hoc for possible non-normal distribution, alpha error ≤0.05).

Results
The Table reports demographics and clinical characteristics of patients entering the study.

PG consisted of instant lottery scratch games in all patients. Six patients also gambled on slot machines. Average daily expenditures (as percentage of daily salary) are reported in the Table.

PG had appeared in all patients in the past year and was a constant problem, as evidenced by DSM-IV and SOGS. In all patients, initial attempts to reduce/switch DA to L-dopa or change DA, gambling counseling, and behavioral strategies had been unsuccessful. PG had appeared in patients with different PD characteristics, as reported in the Table. Five patients dropped out from the study because of side effects consisting of confusion, orthostatic hypotension, insomnia (2 patients), and visual hallucinations, all on amantadine branches (Supplementary Patient Data show further details).

Amantadine abolished daily expenditures, resolving PG in 7 patients; in 5 patients, amantadine reduced G-SAS and Y-BOCS scores, daily expenditures (by 75–90%), and time spent gambling.

Amantadine effect was evidenced on day 2 to 4 of treatment (see Table); as assessed by diaries and caregiver interviews, it was equally effective in the run-in and in the second period of the crossover. Supplementary Figures 1 to 4 show reduction of daily expenditure as percentage of monthly salary. Placebo had no effect in run-in and in-

FIGURE 1: (A) Symptom Assessment Scale (SAS) and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score changes during the crossover study. Both scores are reduced by amantadine (p < 0.001 compared to baseline). Baseline indicates scores (averaged for each patient) in T1, T2; placebo (P) and amantadine (A) scores indicate averaged scores in T3 and T5 of the crossover. (B) SAS and Y-BOCS score changes during the open study in the 7 patients treated with placebo in T5 (second crossover branch). Notice that reductions of SAS and Y-BOCS scores persisted from T6 to the end of study, T7 (p < 0.01). (C) Y-BOCS subitem 6 (time spent gambling) reported throughout the crossover and open extension study (periods T1–T7). White bars at T1, T2, and T4 indicate periods without pathological gambling (PG) treatments. Notice that PG scores are reduced by amantadine during the crossover study (T3 and T5), whereas placebo (T3, T5) has no effect. T6 and T7 show a preserved effect of amantadine administration during the open follow-up. Notice that during the T4 washout period, PG scores increase in 1 week, evidencing the short-lived effect of amantadine (Supplementary Figs 1–4 detail the finding).
duced reoccurrence of PG in 2 to 3 days during switchover. In patients receiving placebo during the T3 and T5 crossover period, G-SAS and Y-BOCS scores and daily expenditures were at the same level as in baseline.

Comparison of G-SAS, Y-BOCS, and total gambling expenditures between amantadine and placebo revealed a probability of \( p < 0.01 \) (see Table, Fig, and Supplementary Figs 1–4).

G-SAS and Y-BOCS scores after 2 weeks of amantadine treatment were reduced by 80% compared to baseline, whereas no changes occurred during the placebo treatment (see Fig 1A). Differences between treatments in the crossover study were statistically significant (G-SAS: \( F = 522.9; \ p < 0.001 \); Y-BOCS: \( F = 698.2; \ p < 0.001 \)), regardless of whether dropped-out patients were included. No carryover effect was observed (G-SAS: \( F = 0.17; \ p = 0.69 \); Y-BOCS: \( F = 1.59; \ p = 0.17 \)). Supplementary Statistical Data provide a detailed analysis.

Figure 1B shows scale score changes during open follow-up branches. A reduction of the G-SAS (\( p < 0.001 \)) and Y-BOCS scores (\( p < 0.001 \)) was observed in both assessments of open study (T6 and T7) in the 7 patients treated with placebo in the second phase of the crossover study.

Timing of amantadine effect is evidenced in Supplementary Figures 1–4 and in Figure 1C, showing incremental increase of time spent gambling during the 1-week washout T4 period in comparison with study effects.

No patient had side effects because of amantadine withdrawal.

**Discussion**

The effect of amantadine was beyond expectations, as a financially devastating compulsive behavior was completely abolished or markedly reduced in all patients. Evidence of this effect might help neurologists who are forced to deal with PD patients affected by PG. Compulsive gambling is a major problem only in a restricted percentage of PD patients, yet it has led worldwide to litigation, including accusations of inadequate management of antiparkinsonian treatments, on the assumption of its relationship with DA.\(^4\)

Amantadine is an old drug showing surprising new qualities; its effect on dyskinesias was discovered only a few years ago,\(^11,21\) and its effect on behavioral disorders in PD has not been addressed, except for anecdotic reports describing occurrence of confusion, psychosis, or hallucinations during its use.\(^22,23\) Hallucinations and confusion appeared also during our study, leading to premature withdrawal of the drug in 5 patients, providing evidence that amantadine might be poorly tolerated in PD patients with PG (29.4%), as in the general PD population. Theoretical issues suggest that amantadine might induce psychosis because of its antiglutamatergic activity\(^24\) and thus might be contraindicated in patients at risk of, or already affected by, behavior disorders. Contrasting with this assumption, the present report showed that PG could be suppressed in 2 to 3 days by amantadine and that amantadine withdrawal induced, in a few days, reappearance of the disorder. This short time effect of amantadine on PG suggests that synaptic remodulation of glutamate/dopamine imbalance is the most likely mechanism in agreement with the introductory hypotheses, whereas plastic reorganization would require longer exposition time. The effect of amantadine gives new perspectives for research on understanding and treatment of PG.

**Acknowledgment**

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**Potential Conflicts of Interest**

Nothing to report.

**References**


