ORIGINAL ARTICLE

# Impulse control disorder related behaviours during long-term rotigotine treatment: a *post hoc* analysis

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**Keywords:**
clinical trial, dopamine agonists, impulse control disorders, long-term treatment, Parkinson's disease, rotigotine transdermal patch

Received 18 May 2016
Accepted 9 June 2016

*European Journal of Neurology* 2016, **23:** 1556–1565

doi:10.1111/ene.13078

**Background and purpose:** Dopamine agonists in Parkinson's disease (PD) are associated with impulse control disorders (ICDs) and other compulsive behaviours (together called ICD behaviours). The frequency of ICD behaviours reported as adverse events (AEs) in long-term studies of rotigotine transdermal patch in PD was evaluated.

**Methods:** This was a *post hoc* analysis of six open-label extension studies up to 6 years in duration. Analyses included patients treated with rotigotine for at least 6 months and administered the modified Minnesota Impulse Disorders Interview. ICD behaviours reported as AEs were identified and categorized.

**Results:** For 786 patients, the mean (±SD) exposure to rotigotine was 49.4 ± 17.6 months. 71 (9.0%) patients reported 106 ICD AEs cumulatively. Occurrence was similar across categories: 2.5% patients reported 'compulsive sexual behaviour', 2.3% 'buying disorder', 2.0% 'compulsive gambling', 1.7% 'compulsive eating' and 1.7% 'punding behaviour'. Examining at 6-month intervals, the incidence was relatively low during the first 30 months; it was higher over the next 30 months, peaking in the 54–60-month period. No ICD AEs were serious, and 97% were mild or moderate in intensity. Study discontinuation occurred in seven (9.9%) patients with ICD AEs; these then resolved in five patients. Dose reduction occurred for 23 AEs, with the majority (73.9%) resolving.

**Conclusions:** In this analysis of >750 patients with PD treated with rotigotine, the frequency of ICD behaviour AEs was 9.0%, with a specific incidence timeline observed. Active surveillance as duration of treatment increases may help early identification and management; once ICD behaviours are present rotigotine dose reduction may be considered.

## Introduction

Impulse control disorders (ICDs), such as pathological gambling, hypersexuality, compulsive shopping and compulsive eating, and other compulsive behaviours, such as punding and hobbyism (together hereafter referred to as 'ICD behaviours' or 'ICDs'), are an increasingly recognized psychiatric complication in patients with Parkinson's disease (PD) [1–3]. These behaviours encompass a wide range of severity, but in general they are associated with a decreased quality of life [4], greater functional impairment [5] and increased caregiver burden [6]. Thus, patient and caregiver education is important, as is routine monitoring for their early detection [1,3]. The DOMINION study, a cross-sectional, observational study of 3090 patients treated with a PD medication for at least 1 year, reported an overall point prevalence estimate of 13.6% [2]; however, the prevalence varies between studies because of differences in assessment methods and the sociocultural background of the study populations [3,7,8].

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Parkinson's disease itself does not appear to confer an increased risk for development of ICD behaviours [9–11], and introduction of medication is likely to be the primary risk factor, with the strongest association reported for dopamine agonists (DAs) [2,12–15]. For example, the DOMINION study reported a prevalence of 17.1% in treated PD patients receiving a DA versus 6.9% in treated PD patients not receiving a DA [2]. Longer duration of DA treatment may increase ICD risk [16,17].

Rotigotine is a non-ergot DA administered via a transdermal patch to provide continuous drug delivery with stable plasma levels over 24 h [18]. It has been hypothesized that ICD development might be enhanced by pulsatile receptor stimulation and that continuous drug delivery may be associated with lower risk [19]. However, the occurrence of ICD behaviours in the context of clinical studies and with long-term exposure to rotigotine, or any other DA, has not been reported. The objective of this *post hoc* analysis was to evaluate the frequency of ICD behaviours reported as adverse events (AEs) in long-term studies (up to 6 years in duration) of rotigotine transdermal patch in PD.

## Methods

### Studies included

This *post hoc* analysis was based on pooled data from six open-label extension studies of rotigotine in patients with PD across different disease stages and severity. Detailed methods for each of these studies have been reported [20–23]. The main characteristics of the studies in this analysis, including the key inclusion criteria, are reported in Table 1. Only one study specified an exclusion criterion directly related to ICDs: patients were excluded from the RECOVER study if they had evidence of an ICD according to the modified Minnesota Impulsive Disorders Interview (mMIDI) at screening. All studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and were approved by the relevant institutional review boards or ethics committees; written informed consent was obtained from all patients prior to participation.

During the open-label extension studies, patients received optimal dose rotigotine (up to 16 mg/24 h); dose adjustments of rotigotine for efficacy or tolerability were permitted at any time at the discretion of the investigator. In addition, concomitant levodopa was also permitted.

### Subgroup of patients included

The Minnesota Impulsive Disorders Interview (MIDI) is a screening tool used to monitor the presence of ICDs; the MIDI or modified versions have been used previously in studies of patients with PD [2,11,14,24]. In these six open-label studies, a mMIDI was used as a surveillance tool to screen for possible ICDs; it served to prompt investigators to monitor for the presence of ICD behaviours, and therefore also enhanced the detection and reporting of AEs indicative of these behaviours. The mMIDI included queries for the presence of the five most common ICD behaviours associated with DA use: 'buying disorder', 'compulsive gambling', 'compulsive sexual behaviour', 'compulsive eating' and 'punding behaviour'.

In the current analyses, our focus was on the subgroup of patients who were administered the mMIDI during open-label rotigotine treatment, with the aim of reporting data from a cohort of patients screened for ICD behaviours. In addition, as longer duration of treatment with DAs has been shown to contribute to the risk of ICD development [16,17], patients who had received long-term (i.e. at least 6 months) rotigotine treatment were our specific focus. ICD behaviour AEs (ICD AEs) were therefore analysed for the subgroup of patients who (i) received rotigotine for at least 180 days (~6 months) and (ii) were also administered the mMIDI at any time point during the study. In the majority of the studies (SP702, SP716, SP715 and SP516) the mMIDI was administered at ~3-month intervals during maintenance starting from the ~15-month maintenance visit (~9-month visit in SP833). In SP915 the mMIDI was administered at the start of maintenance and at the ~4-month and ~8-month maintenance visits. In all studies, the mMIDI was also administered at the end of treatment or early withdrawal and safety follow-up visits. The mMIDI was introduced to some of the studies as a protocol amendment after the studies had already been initiated.

### *Post hoc* analysis of ICD-related behaviours

Impulse control disorder AEs were originally defined according to the Medical Dictionary for Regulatory Activities (MedDRA version 9.1) Preferred Terms and included typical ICDs and other impulsive behaviours; obsessive–compulsive disorder and other obsessive behaviours, although are not classified as ICDs, were included in order to capture all potentially behaviourally relevant AEs.

**Table 1** The main characteristics of the six open-label extension studies included in the *post hoc* analysis

| Open-label extension study | SP702 [20] (NCT00594165) $n$ = 216 | SP716 [22] (NCT00599196) $n$ = 380 | SP715 [23] (NCT00594386) $n$ = 258 | SP516 [23] (NCT00501969) $n$ = 395 | SP915 [21] (NCT00519532) $n$ = 84 | SP833 [25] (NCT00505687) $n$ = 186 |
|---|---|---|---|---|---|---|
| Study duration | Up to 6 years | | | Up to 4 years | Up to 1 year | Up to 3.5 years |
| Rotigotine dosing | Optimal dose: ≤6 mg/24 h year 1, ≤16 mg/24 h thereafter | Optimal dose: ≤8 mg/24 h year 1, ≤16 mg/24 h thereafter | Optimal dose: ≤16 mg/24 h | | | |
| Levodopa use | Concomitant levodopa permitted (after 1 month open-label maintenance) | | Concomitant levodopa permitted | | | |
| Previous study | SP512 (early PD) | SP513[a] (early PD) | PREFER (advanced PD) | CLEOPATRA-PD[b] (advanced PD) | RECOVER (PD with early morning motor impairment) | SP824 (PD) and SP825 and SP826 (PD with early morning motor impairment) |
| Study design | Double-blind, randomized, placebo controlled | | | | | Open-label |
| Rotigotine dosing | Optimal dose: 2–6 mg/24 h | Optimal dose: 2–8 mg/24 h | Fixed dose: ≤8 or ≤12 mg/24 h | Optimal dose: 4–16 mg/24 h | Optimal dose: 2–16 mg/24 h | Optimal dose: 4–8 mg/24 h (SP824) 2–8 mg/24 h (SP825) 2–16 mg/24 h (SP826) |
| Rotigotine maintenance phase | 24 week | 33 week | 24 week | 16 week | 4 week | 4 week |
| Key inclusion criteria | • Aged ≥30 years<br>• PD ≤5 years<br>• Hoehn and Yahr ≤3<br>• Levodopa not permitted | | • Aged ≥30 years<br>• PD ≥3 years<br>• Hoehn and Yahr 2–4<br>• Inadequately controlled on stable levodopa | | • Aged ≥18 years<br>• PD and unsatisfactory early morning motor impairment<br>• Hoehn and Yahr 1–4<br>• Levodopa permitted (at stable dose) | • Aged ≥18 years<br>SP824:<br>• PD<br>• Hoehn and Yahr 1–4<br>• Levodopa permitted (at stable dose)<br>SP825:<br>• PD ≤5 years and unsatisfactory early morning motor impairment<br>• Hoehn and Yahr 1–3<br>• Levodopa not permitted<br>SP826:<br>• PD and unsatisfactory early morning motor impairment<br>• Hoehn and Yahr 1–4<br>• Levodopa permitted (at stable dose) |

PD, Parkinson's disease.
[a]SP513 also included a ropinirole arm; [b]CLEOPATRA-PD also included a pramipexole arm.

The ICD AEs were then categorized by medical review into the five most common ICD behaviours associated with DA use. This clinically driven medical review comprised allocating the investigator's reported term of the AE to the most appropriate of the following: 'buying disorder', 'compulsive gambling', 'compulsive sexual behaviour', 'compulsive eating' and 'punding behaviour'. If the reported term of the AE was not considered to correspond to one of these categories, it was assigned to 'other'; the latter category included obsessive–compulsive disorder.

The frequency, seriousness, intensity, study discontinuations (and rotigotine dose reductions) due to ICD AEs, and outcome are reported. The time course of the first AE by duration of exposure to rotigotine (analyses by 6-month rotigotine exposure intervals) and frequency by rotigotine dose and concomitant levodopa use are also reported. All analyses were performed descriptively.

## Results

### Patients

Of the 2203 patients randomized/treated in the preceding double-blind/open-label studies, 1763 (80.0%) patients completed the preceding studies, and 1519 (69.0% of those randomized/treated, or 86.2% of those completing the preceding double-blind/open-label studies) entered the long-term open-label extensions. A total of 786 patients were administered the mMIDI and received open-label rotigotine for at least 6 months. Demographics and baseline characteristics are reported in Table 2. Patients had a mean (±SD) time of exposure to open-label rotigotine of 49.4 (±17.6) months (median 52.9 months; range 6.2–74.2 months).

### Overall cumulative frequency of ICD behaviours

Of the 786 patients, 71 (9.0%) patients reported a total of 106 ICD AEs over time. None of the reported ICD AEs were considered to be serious by the investigator. Of the 106 AEs occurring in 71 patients, the vast majority (103; 97%) were considered mild (54; 51%) or moderate (49; 46%) in intensity, and only in three patients severe: 'buying disorder' (one patient), 'compulsive gambling' (one patient) and 'punding behaviour' (one patient).

### Comparison of different ICD categories

The frequency was similar across the ICD categories (Fig. 1; Table 3). A total of 16 of the 71 (22.5%)

**Table 2** Demographics and baseline characteristics[a]

| | All patients $n = 786$ | Patients who reported ICD $n = 71$ | Patients who did not report ICD $n = 715$ |
|---|---|---|---|
| Age, mean ± SD (range), years | 63.0 ± 9.7 (31–87) | 56.9 ± 9.6 (35–81) | 63.7 ± 9.4 (31–87) |
| <75 years, *n* (%) | 698 (88.8) | 69 (97.2) | 629 (88.0) |
| ≥75 years, *n* (%) | 88 (11.2) | 2 (2.8) | 86 (12.0) |
| Male, *n* (%) | 510 (64.9) | 48 (67.6) | 462 (64.6) |
| Caucasian | 744 (94.7) | 67 (94.4) | 677 (94.7) |
| Time since PD diagnosis, mean ± SD (range), years | 4.9 ± 4.5 (0–25) | 4.7 ± 4.2 (0–16) | 4.9 ± 4.6 (0–25) |
| Hoehn and Yahr stage[c], *n* (%) | | | |
| 1 | 100 (12.7) | 11 (15.5) | 89 (12.4) |
| 2 | 418 (53.2) | 46 (64.8) | 372 (52.0) |
| 3 | 184 (23.4) | 13 (18.3) | 171 (23.9) |
| 4 | 11 (1.4) | 1 (1.4) | 10 (1.4) |
| UPDRS II, mean ± SD[b] | 10.7 ± 5.5 | 11.2 ± 5.9 | 10.6 ± 5.4 |
| UPDRS III, mean ± SD[b] | 24.3 ± 11.6 | 26.1 ± 12.0 | 24.1 ± 11.6 |
| Concomitant levodopa use | | | |
| Received levodopa at any point during studies, *n* (%) | | 67 (94.4) | 627 (87.7) |
| Were receiving levodopa at ICD AE onset, *n* (%)[d] | | 63 (88.7) | N/A |
| Levodopa dose over entire studies, mean ± SD, mg/day | | 1033.6 ± 734.75 ($n = 67$) | 875.9 ± 577.12 ($n = 575$)[e] |
| Levodopa dose at ICD AE onset, mean ± SD, mg/day[f] | | 1203.4 ± 851.47 ($n = 62$) | N/A |

AE, adverse event; ICD, impulse control disorder; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.
[a]Baseline values from preceding double-blind/open-label studies reported; [b]except for UPDRS in SP915 where baseline is first titration visit of open-label extension; [c]Hoehn and Yahr stage was not assessed in SP915; data missing from 73 patients; [d]levodopa intake was considered concomitant if AE onset occurred between the start and end of levodopa intake; if concomitance could not be determined due to missing/partial dates, the intake was considered concomitant; [e]levodopa dose could not be calculated for 52 patients; [f]if a patient experienced >1 ICD AE, the levodopa dose at the time of the first AE was utilized; levodopa dose could not be calculated for one patient.

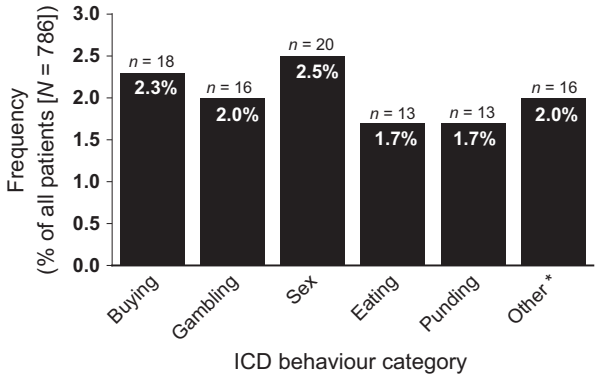


**Figure 1** Frequency of the different impulse control disorder (ICD) categories. *n*, number of patients who reported at least one ICD adverse event; *N*, total number of patients. *'Other' includes investigator reported terms: compulsive behaviour/s, compulsive disorder, impulse control disorder, impulsive behaviour, impulsive control behaviour/s, obsessive–compulsive behaviour, obsessive–compulsive disorder, poor impulse control.

patients reported more than one category of ICD behaviour (10 patients reported two types, three patients reported three types and three patients reported four types). A total of 17 ICD AEs reported in 16 of the 71 (22.5%) patients were not considered to correspond to one of the distinct categories and were assigned to the 'other' category. These included the reported terms impulse control disorder (one AE), impulsive control behaviour/s (two AEs), poor impulse control (one AE), impulsive behaviour (two AEs), obsessive–compulsive disorder (one AE), obsessive–compulsive behaviour (one AE), compulsive disorder (one AE) and compulsive behaviour/s (eight AEs).

### Action taken with rotigotine and outcome of ICD behaviours

A total of 60 of the 106 (57%) ICD AEs resolved, seven (7%) resolved with sequelae (not specified) and 37 (35%) were not resolved at the time of study closure.

*Impulse control disorder behaviours leading to study discontinuation*

Nine of the 106 (8.5%) ICD AEs led to study discontinuation in seven of the 71 (9.9%) patients with an ICD AE, corresponding to <1% (7/786) of all patients included in analyses. These ICD behaviours resolved after study discontinuation in five of the seven patients: 'buying disorder' (one patient), 'compulsive sexual behaviour' (two patients) and 'other' (two patients; investigator's reported terms: compulsive behaviour and impulsive control behaviours). They did not resolve after study discontinuation in two of the seven patients: combination of 'compulsive

**Table 3** Frequency of ICDs by rotigotine modal dose[a]

| | Rotigotine modal dose, mg/24 h; *n* (%) [ICD AEs] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2<br>*N* = 9 | 4<br>*N* = 31 | 6<br>*N* = 95 | 8<br>*N* = 138 | 10<br>*N* = 90 | 12<br>*N* = 108 | 14<br>*N* = 77 | 16<br>*N* = 238 | Overall<br>*N* = 786 |
| Any ICD behaviour reported as AEs | 0 | 2 (6.5) [3] | 14 (14.7) [16] | 14 (10.1) [26] | 10 (11.1) [14] | 10 (9.3) [20] | 9 (11.7) [14] | 12 (5.0) [14] | 71 (9.0) [106] |
| Categorized | | | | | | | | | |
| Compulsive sexual behaviour | 0 | 0 | 4 (4.2) | 3 (2.2) | 5 (5.6) | 2 (1.9) | 4 (5.2) | 2 (0.8) | 20 (2.5) [22] |
| Buying disorder | 0 | 1 (3.2) | 2 (2.1) | 6 (4.3) | 2 (2.2) | 1 (0.9) | 3 (3.9) | 3 (1.3) | 18 (2.3) [20] |
| Compulsive gambling | 0 | 1 (3.2) | 3 (3.2) | 4 (2.9) | 2 (2.2) | 4 (3.7) | 1 (1.3) | 1 (0.4) | 16 (2.0) [20] |
| Punding behaviour | 0 | 0 | 1 (1.1) | 3 (2.2) | 2 (2.2) | 3 (2.8) | 0 | 4 (1.7) | 13 (1.7) [14] |
| Compulsive eating | 0 | 0 | 1 (1.1) | 1 (0.7) | 2 (2.2) | 5 (4.6) | 2 (2.6) | 2 (0.8) | 13 (1.7) [13] |
| Other[b] | 0 | 0 | 4 (4.2) | 3 (2.2) | 1 (1.1) | 4 (3.7) | 2 (2.6) | 2 (0.8) | 16 (2.0) [17] |

AE, adverse event; ICD, impulse control disorder; *n*, number of patients who reported at least one ICD AE; %, percentage of patients amongst total *N*; [ICD AEs], number of individual ICD AEs occurring amongst the *n* patients.
[a]Modal dose, defined as the most frequently used daily dose over the observation period; [b]'Other' includes reported terms: compulsive behaviour/s, compulsive disorder, impulse control disorder, impulsive behaviour, impulsive control behaviour/s, obsessive–compulsive behaviour, obsessive–compulsive disorder, poor impulse control.

gambling', 'punding behaviour' and 'compulsive eating' (one patient); and 'other' (one patient; investigator's reported term: compulsive behaviours).

*Impulse control disorder behaviours leading to rotigotine dose reduction*

Twenty-three of the 106 (21.7%) ICD AEs led to a reduction in rotigotine dose in 17 of the 71 (23.9%) patients; of these, 17 resolved (in 14 patients), four resolved with sequelae (in two patients) and two were not resolved (in two patients).

*No action taken with rotigotine*

For 66 of the 106 (62.3%) ICD AEs in 51 (71.8%) patients, no change was made to the dose of rotigotine; of these, 32 resolved (in 28 patients), three resolved with sequelae (in three patients), 29 were not resolved at the time of study closure (in 23 patients) and two were lost to follow-up (in one patient).

### Impulse control disorder behaviours by duration of exposure to rotigotine, rotigotine dose and concomitant levodopa use

*Time course to first ICD AE onset by length of exposure to rotigotine*

The percentage of incident (i.e. new) ICD cases was relatively low and stable during the 6-month intervals over the first 30 months of open-label rotigotine exposure, with between 0.5% and 0.8% of patients reporting their first ICD AE during each 6-month interval. The percentage of incident cases became higher over the following 30 months of treatment, ranging from 0.9% to 2.9% per 6-month interval, and peaked during the 54–60-month period (Fig. 2a). The cumulative frequency of the ICD AEs is shown in Fig. 2b.

*Rotigotine dose*

There was no association between the frequency of ICD AEs and the modal dose of rotigotine throughout the entire exposure period (Table 3). The frequency was also assessed according to the dose of rotigotine at the time of first reported ICD AE, as dose adjustments of rotigotine were permitted at any time during the open-label extension studies. There was an increase in overall ICD AEs with increasing dose of rotigotine. A noticeable increase in overall ICD AEs was first apparent at the 8 mg/24 h dose. This was also evident specifically for 'compulsive sexual behaviour' (an increase first noted at the 12 mg/24 h dose), but not for the other ICD categories (Table 4).

*Concomitant levodopa use*

Of the 71 patients who reported ICD AEs, 94.4% had concomitant levodopa at any point during the studies (88.7% were receiving levodopa at the time of AE onset); 87.7% patients who did not report ICD AEs received concomitant levodopa during the study (Table 2). The mean (±SD) daily dose of levodopa was numerically higher in the patients who reported ICD AEs, for dose both over the entire study and at AE onset (Table 2).

### Clinical and demographic characteristics associated with ICD AEs

Demographics and baseline characteristics by ICD AE status are reported in Table 2. There was a slightly higher proportion of males than females [48/510 males, 9.4% vs. 23/276 females, 8.3%; $P = 0.6146$ (exploratory chi-squared)], and patients who reported these AEs were younger [age, mean (±SD): 56.9 (±9.6) vs. 63.7 (±9.4) years; $P < 0.0001$ (exploratory $t$ test)] and reported slightly more severe Unified Parkinson's Disease Rating Scale III (motor) scores [26.1 (±12.0) vs. 24.1 (±11.6); $P = 0.1672$ (exploratory $t$ test)] (Table 2).

## Discussion

In this *post hoc* analysis of over 750 patients with PD who were treated with rotigotine transdermal patch for between 6 months and 6 years, the overall frequency of ICD behaviours reported as AEs was 9.0%. The observed ICDs – compulsive gambling, sexual behaviour, shopping, eating and punding – are in accordance with those recognized and reported most commonly in patients with PD receiving DAs [1–3]. In this analysis, the frequency of the different behaviours was largely similar ('compulsive eating' 1.7%, 'punding' 1.7%, 'compulsive gambling' 2.0%, 'buying disorder' 2.5%, 'compulsive sexual behaviour' 2.5%). The proportion of patients with an ICD who reported two or more types of behaviours was also similar to that reported in the DOMINION study (~23% vs. ~29%) [2].

None of the ICD AEs were considered serious, and only three were reported to be severe in intensity. Moreover, in five of the seven patients who discontinued the drug due to these AEs a complete resolution of symptoms was reported. Of note, the majority of the 17 patients whose dose of rotigotine was reduced also recovered from the ICD behaviour. Although no conclusions can be reached on any dose–response relationship between rotigotine and ICDs, interestingly the overall prevalence of ICD AEs appeared to

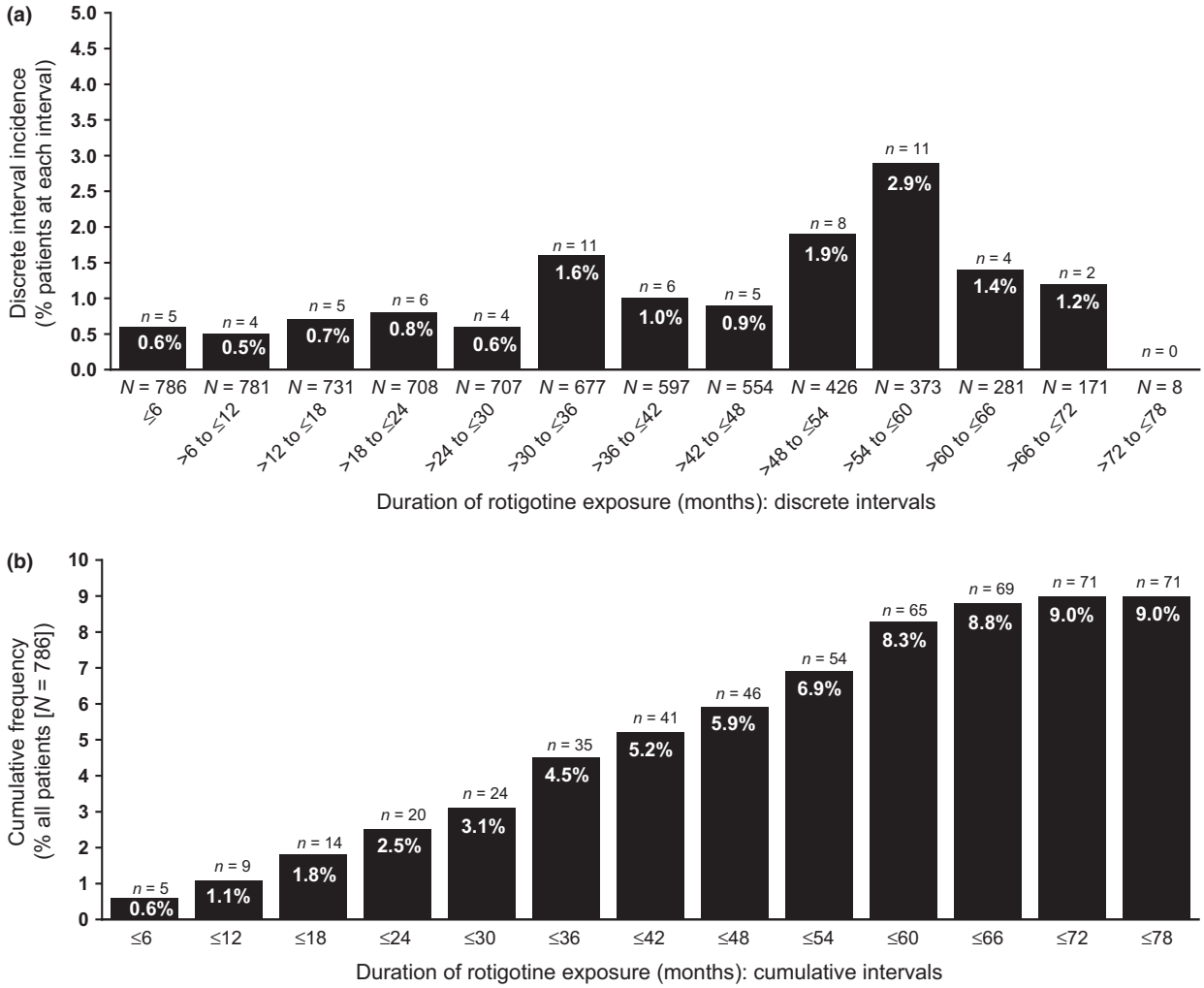


**Figure 2** Impulse control disorders (ICDs) by duration of rotigotine exposure (6-month intervals). (a) Discrete interval incidence. *n*, number of patients reporting their first ICD during the interval; *N*, the total number of patients at risk of reporting their first adverse event (AE) (included those who received rotigotine during the interval and had not previously reported their first AE during an earlier interval). (b) Cumulative interval frequency. *n*, number of patients who reported at least one AE; *N*, total number of patients.

**Table 4** Frequency of ICDs by rotigotine dose at AE onset

| | Rotigotine dose at AE onset, mg/24 h; *n* (%) [ICD AEs] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2<br>*N* = 403 | 4<br>*N* = 737 | 6<br>*N* = 743 | 8<br>*N* = 730 | 10<br>*N* = 622 | 12<br>*N* = 543 | 14<br>*N* = 409 | 16<br>*N* = 310 |
| Any ICD behaviour reported as AEs | 6 (1.5) [6] | 6 (0.8) [9] | 8 (1.1) [9] | 16 (2.2) [18] | 13 (2.1) [15] | 12 (2.2) [15] | 13 (3.2) [22] | 11 (3.5) [12] |
| Categorized | | | | | | | | |
| Compulsive sexual behaviour | 1 (0.2) | 0 | 2 (0.3) | 3 (0.4) | 3 (0.5) | 5 (0.9) | 6 (1.5) | 2 (0.6) |
| Buying disorder | 2 (0.5) | 0 | 3 (0.4) | 2 (0.3) | 3 (0.5) | 1 (0.2) | 6 (1.5) | 2 (0.6) |
| Compulsive gambling | 2 (0.5) | 2 (0.3) | 1 (0.1) | 6 (0.8) | 2 (0.3) | 3 (0.6) | 1 (0.2) | 1 (0.3) |
| Punding behaviour | 1 (0.2) | 2 (0.3) | 1 (0.1) | 1 (0.1) | 1 (0.2) | 3 (0.6) | 2 (0.5) | 3 (1.0) |
| Compulsive eating | 0 | 3 (0.4) | 1 (0.1) | 1 (0.1) | 2 (0.3) | 1 (0.2) | 3 (0.7) | 2 (0.6) |
| Other[a] | 0 | 2 (0.3) | 1 (0.1) | 4 (0.5) | 3 (0.5) | 2 (0.4) | 3 (0.7) | 2 (0.6) |

AE, adverse event; ICD, impulse control disorder; *n*, number of patients who reported at least one ICD AE; %, percentage of patients amongst total *N*; [ICD AEs], number of individual ICD AEs occurring amongst the *n* patients.

[a]'Other' includes reported terms: compulsive behaviour/s, compulsive disorder, impulse control disorder, impulsive behaviour, impulsive control behaviour/s, obsessive–compulsive behaviour, obsessive–compulsive disorder, poor impulse control.

increase starting at a dose of 8 mg/24 h, and at 12 mg/24 h for 'compulsive sexual behaviour' specifically. This suggests that a specific threshold dose may exist and has clinical consequences since a dose reduction may be initially considered in selected cases. Indeed, small observational studies have also reported that DA dose reduction may lead to improvement in many patients [26,27].

The mean duration of treatment with open-label rotigotine was approximately 4 years. The time course of ICD AE onset was variable, but the number of incident cases during the first 30 months was low and increased afterwards. As ICDs are becoming increasingly recognized in PD, it cannot be excluded that reporting bias may have contributed to this increase. However, these results are in line with data suggesting that longer duration of treatment with DAs increases the risk of ICDs [16], as well as with a prospective cohort study which reported a median time of 23.0 months after DA initiation to ICD onset [17]. These observations suggest a lag time to ICD onset in many cases. The reasons for this are unclear but may be related in part to increased absolute as well as cumulative DA exposure over time.

In the current analysis, there was a similar proportion of patients receiving concomitant levodopa in each patient group; however, the mean dose of levodopa was numerically higher in those who reported ICD AEs. This is consistent with previous demonstrations that use of levodopa and its absolute dose are independently associated with ICDs [2,28]. Other similar predisposing demographic variables were younger age and male gender [2,3].

As no comparator groups were included in any of the open-label studies in the analyses, no direct comparisons of the prevalence, frequency, type, seriousness/intensity or management of ICD behaviours can be made with other anti-Parkinson medications or placebo. Moreover, as there is no universal definition of ICDs in PD, and as there are various methods used to assess ICDs [such as AEs, detailed interview, mMIDI, or Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease (QUIP)] there is a wide range in the reported ICD rates in this population. ICDs have previously been reported in patients receiving rotigotine (small retrospective case studies), foremost in patients with PD [29] but also in those with restless legs syndrome [30]. A number of epidemiological and cross-sectional studies have also reported the rate of ICDs in PD patients treated with rotigotine or oral DAs [10,31,32]. One such study reported that treatment with an oral DA (pramipexole or ropinirole) was associated with a higher risk of ICD compared with rotigotine transdermal patch [31]. Moreover, a higher rate of ICDs has also been reported with both oral immediate release DAs (pramipexole or ropinirole) and extended release ropinirole compared with rotigotine transdermal patch and extended release pramipexole [32]. However, in these studies the length of exposure varied between the different DAs, which may have played a role in the relative risk for ICDs [31,32]. Therefore, these observations should be confirmed in controlled, head-to-head and specifically designed studies.

A limitation of the majority of previous studies is the cross-sectional observational design; these can only identify the prevalence and clinical correlates of ICDs, but not ICD incidence or specific PD treatment risk factors. No previously published study reporting the occurrence of ICDs in patients with PD (i) has prospectively analysed this large population of patients with PD (>750 patients) enrolled in clinical research, (ii) for this long (up to 6 years follow-up) or (iii) with a specific DA, or has reported (iv) the time course to first ICD onset (i.e. incidence), (v) specific DA treatment ICD risk factors (e.g. rotigotine dose and treatment duration) or (vi) action taken with DA (rotigotine), and ICD outcome. However, there are also a number of limitations. First, not all patients included in the analyses received rotigotine for the full 6 years, so this precluded a comprehensive longitudinal analysis of the entire study cohort. Secondly, the studies relied on AE reporting by patients to detect ICD behaviours, which may have led to underreporting [33]. Also, the reported term of the AE was at the discretion of the site study investigator. Although the mMIDI was used to enhance detection and reporting, it was introduced in some of the open-label extension studies after their initiation. Thus, not all patients would have received serial ICD surveillance by the mMIDI from the start. Moreover, the mMIDI has not been fully validated for use in PD. Finally, selection bias may have occurred in the studies (e.g. only those who successfully completed the preceding double-blind studies/open-label studies were included in the open-label extensions, and the study population included in clinical trials is generally younger and not representative of the PD population at large). However, this analysis did include over 750 patients across different disease stages and with a wide range of symptom severity, and thus represents a broad sample of patients with PD.

In conclusion, in this *post hoc* analysis of over 750 patients with PD treated long term with rotigotine transdermal patch, the cumulative frequency of ICD behaviours reported as AEs was 9.0%. Ongoing active

surveillance, especially as the duration and dose of rotigotine treatment increases, may help early identification and management. A reduction in rotigotine dose may be considered as an initial treatment approach.

## Acknowledgements

The authors thank the patients and their caregivers in addition to the investigators and their teams who contributed to the studies included in these analyses. The authors also acknowledge Emily Thompson, PhD, CMPP (Evidence Scientific Solutions, London, UK), for writing assistance which was funded by UCB Pharma, Brussels, Belgium; Cédric Laloyaux, PhD, CMPP (Strategic Publication Lead Neurology, UCB Pharma, Brussels, Belgium), for publication coordination; Elisabeth Dohin, MD (UCB Pharma, Brussels, Belgium), for scientific and medical input into the data analyses and interpretation; and Marc Derycke, MSc (UCB Pharma, Monheim am Rhein, Germany), for his contributions to the specifications and programming of the *post hoc* analyses. This *post hoc* analysis was supported by UCB Pharma, Monheim am Rhein, Germany.

## Disclosure of conflicts of interest

Angelo Antonini has received consultancy fees/honoraria from AbbVie, UCB Pharma, Mundipharma, Boston Scientific and Zambon. K Ray Chaudhuri has received research support from UCB Pharma, AbbVie and Britannia Pharma 2006–2011; consultancy fees/honoraria from UCB Pharma, AbbVie, US WorldMeds, Otsuka, Mundipharma and Britannia; provides a consultant/advisory role for AbbVie (2010–current), Britannia (2009–current), Mundipharma (2012–current), UCB Pharma (2010–current); receives funding for speaker activities for AbbVie, Britannia, Mundipharma, UCB Pharma, Zambon and Medtronics; receives educational grants from AbbVie, Britannia, Medtronics and UCB Pharma; grants/honoraria from the NIHR, Parkinson's UK, EU, AbbVie, Britannia, Medtronics and UCB Pharma; holds a patent for a product referred to in the CME/CPD programme that is marketed by a commercial organization; and is currently participating in, designing or running a clinical trial (within the past 2 years) for Toledo, Neupark, PANDA and the Newron PDGF study. Daniel Weintraub has received honoraria from UCB Pharma. Babak Boroojerdi, Mahnaz Asgharnejad, Lars Bauer and Frank Grieger are salaried employees of UCB Pharma and receive stock options from this employment.

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