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Sleep Disorders (A Iranzo, Section Editor)

Impulse Control Disorders in REM Sleep Behavior Disorder

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Abstract

Purpose of review This paper reviews clinical and pathophysiological features of both impulse control disorders (ICDs) and REM sleep behavior disorder (RBD) in Parkinson's disease (PD), as well as current evidences of their association. Then, we suggest recommendations to manage PD patients with RBD in order to prevent this potentially devastating psychiatric complication.
Recent findings ICDs are psychiatric complications occurring in patients with Parkinson's disease (PD) treated with dopaminergic replacement therapies (DRT). Besides DRT, risk factors for ICDs are poorly known. We recently showed an association between ICDs and RBD in PD.
Summary Detecting RBD in PD may provide clinician the opportunity to identify patients at higher risk to develop ICDs. In PD patients with either a video-polysomnographic (v-PSG) diagnosis of RBD or a typical history of RBD when v-PSG is not available, dopamine agonists should be avoided whenever possible, or be prescribed at the lowest effective dose. Furthermore, gradual tapering of dopamine agonist would be recommended, due to the potential increased risk of dopamine withdrawal syndrome in these patients. Increased surveillance, implying patients and caregiver education to recognize early changes in behavior and in mood possibly related to a hyperdopaminergic status, should be part of the preventive strategies.

Introduction

Impulse control disorders

Impulse control disorders (ICDs) are a group of increasingly recognized psychiatric complications occurring in patients with Parkinson's disease (PD) treated with dopaminergic replacement therapies (DRT) [1••]. They consist in compulsive and repetitive behaviors that are excessive and/or ultimately harmful to oneself or others and include pathological gambling, compulsive sexual behavior, compulsive buying, eating disorders, and other compulsive-related behaviors [2]. The latter comprise punding, which is an intense fascination with complex, excessive, repetitive, non-goal-oriented behaviors, but also walkabout, excessive hobbyism, and overuse of dopamine replacement therapy, also known as dopamine dysregulation syndrome [3]. The estimated prevalence of ICDs and related behaviors in PD patients is about 14%, while up to 31% of PD patients would experience at least one ICD during the course of their illness [2]. Nevertheless, the prevalence may be much higher according to other reports [4, 5]. On the other hand, ICDs may be also found in general population, with a lower prevalence [6]. These psycho-behavioral behaviors in PD remain underdiagnosed and lack clear recommendations regarding their therapy, yet they may lead to severe social and legal consequences [7–9].

Predisposing factors for ICDs in PD include young age, early onset of PD, longer duration of the disease, a personal or familiar history of addictive behaviors, substance abuse or bipolar disorder, and impulsivity trait.[1] Particularly, high novelty seeking personality traits have also been identified as ICD risk factors, especially in patients with DDS [10, 11]. Novelty seeking is usually associated with increased impulsivity, addiction, and inability to delay gratification [12] and declines with age in healthy populations [13].

Compulsive sexual behavior has been more frequently reported in males, whereas compulsive shopping and binge eating is more common in female PD patients [3, 14], suggesting a possible role of cultural aspects, together with biological factors, in determining the type of ICD. Male gender may also be a risk factor in PD patients for developing pathological gambling (PG) according to some [8, 10] but not all studies [11, 15]. Nevertheless, the majority of PD patients with PG never gambled before taking dopamine agonists [16], and most ICDs are reversible after tapering the dopaminergic medication, suggesting that these behaviors are triggered by changes in baseline dopamine levels in susceptible patients.

The greatest risk factor for the development of ICD in PD is certainly represented by the longer use and higher dose of DRT [17•, 18•, 19],., Furthermore, whereas DDS and punding are more frequently seen in patients taking higher amounts of L-dopa [20], dopamine agonists seem to be more implicated than levodopa in other ICDs [1••]. No difference in the frequency of ICD has been reported between pramipexole and ropinirole [21, 22],. On the other hand, lower rate of ICDs has been reported with long acting or transdermal DA in preliminary observational studies [23, 24],. Besides, the reversibility of ICDs and related behaviors after withdrawal of dopamine agonist has been well documented in several studies [16, 25],.

Regarding non-dopaminergic therapies, the effect of amantadine on ICDs in PD remains debated as it has been found to be associated with a higher risk of ICDs [26], while another study reported an improvement of pathological gambling under amantadine [27]. Parkinson's disease in itself, without DRT, does not appear to confer an increased risk for development of ICDs, since prevalence of ICDs has been reported to be similar in untreated PD compared to general population [28]. On the other hand, ICDs have been reported in patients with conditions other than PD, when treated with dopaminergic agents, such as Restless Legs Syndrome [29, 30], or prolactinoma, which suggest the main role of DRT in the genesis of ICDs independently of the pathology [31]. However, the risk to develop ICDs appears to be increased in PD patients with dopaminergic denervation, compared to RLS patients in which no dopaminergic denervation was observed, suggesting a synergic role of the dopaminergic denervation and the treatment with dopaminergic agents [32•].

Cognitive impairment, namely in executive functions, has been observed in PD patients with ICDs compared to those without [33]. However, some studies found no differences [11] [34], or even better executive functions in PD patients with ICDs [35]. Actually, it has been suggested that impaired executive functions observed in PD patients with ICD could be ascribed to a reversible drug-induced impairment on selective frontal lobe functions in predisposed individuals, rather than a cognitive decline [33, 36–38].

Pathophysiology of ICDs

Pathophysiology of ICDs is complex and not fully understood. Dopaminergic mesocorticolimbic system is known to play a key role in reward and in impulse control regulation. Changes in dopamine transmission at presynaptic and postsynaptic levels after chronic dopaminergic treatment may predispose to the emergence of ICDs via a sensitization of a damaged ventral striatal circuitry [35]. Indeed, functional imaging studies in PD patients with ICDs have demonstrated abnormalities of the reward pathways including the ventral striatum, the cingulate gyrus, and the orbitofrontal cortex, strengthening the links between the ICDs seen in PD and addiction in general [39, 40],. Ventral striatum dopamine release was found increased during a gambling task in PD patients with pathological gambling compared to those without [41], as well as in a group of PD patients with different ICDs following reward-related visual cues [42]. Increase in ventral striatum blood-oxygen-level dependent (BOLD) activity was also found by functional magnetic resonance imaging (fMRI) studies in PD patients with ICDs during gambling-related visual cues [43].

On the other hand, a low ventral striatal D2/D3 receptor availability has been described in [11C] raclopride PET studies, suggesting a sensitization of ventral striatal circuits to reward and a reduced transmission of reward signals (reward deficiency syndrome), leading to increased reward seeking [41] [41],. Taken together, these results are consistent with a global sensitization to appetitive behaviors with dopaminergic therapy in vulnerable individuals.

Furthermore, the potential to induce compulsive behaviors in patients with PD may be related to the involvement of dopamine receptor subtypes. Dopamine agonists such as pramipexole, ropinirole, or rotigotine are relatively selective to dopamine D3 receptors. The dopamine receptor subtypes are unevenly distributed within brain regions. While D1 and D2 receptors are found to be abundant in the dorsal striatum, D3 receptors are found in abundance in the ventral striatum [44], which may explain the increased propensity to induce impulsive behaviors associated to dopamine agonists.

ICDs are associated to levodopa-induced dyskinesia, suggesting a common mechanism of the corticostriatal circuitry in the motor and non-motor domains [45]. Indeed, a unifying view is that the involuntary movements of dyskinesia and behavioral disorders as ICDs, punding, and compulsive medication use are part of a continuum and are motor, cognitive, and emotional pathological expressions, mediated by intrinsically similar physiological mechanism acting through different basal ganglia channels or subregions.

The involvement of dopamine receptors has also been suggested by genetic studies on ICDs in general population, showing polymorphisms of genes implicated in dopamine metabolism pathway (COMT, DAT), or encoding for dopamine receptors (DRD1, DRD2, DRD3, DRD4), serotonin receptors and its transporter (HTR2A, 5HTT), and glutamate receptors (GRIN2B) [46]. In PD, a panel of genes that increases the chance to predict ICDs when considered together with clinical variables has been recently identified [47]..

Management of ICDs mainly relies on tapering DRT. The effectiveness of other pharmacological treatments, including amantadine, serotonin selective reuptake inhibitors, antipsychotics, anticonvulsants, and opioid antagonists (e.g., naltrexone) are uncertain as evidences are still lacking or insufficient [48].

REM sleep behavior disorder

REM sleep behavior disorder is a parasomnia characterized by elaborate behaviors during REM sleep usually associated to action-filled dreams [49]. Dream enactment behaviors result from a loss of abnormal motor control during REM sleep, namely from a loss of muscle atonia and/or an increased phasic muscle activity during this stage.

RBD may occur in isolated form, e.g., not associated to other neurological disorder, and is called idiopathic RBD (iRBD) [50]. However, the vast majority of iRBD patients will eventually develop a neurodegenerative disorder of alpha-synucleine type, in the years following RBD onset [51] [52],.

This condition is therefore currently considered as a prodromal stage of an alpha-synucleinopathy. Up to 60% of Parkinson's disease patients show RBD [53]. Clinical, neuropsychological, and imaging studies consistently show that RBD in PD represents a marker of a malignant phenotype, paralleled by a more widespread degenerative process [54, 55•]. Indeed, PD-RBD patients were shown to have more severe motor signs [56, 57], as well as an increased prevalence of non-motor symptoms [58], including increased levodopa-induced dyskinesia [55•, 59]. In particular, RBD in PD was shown to be associated to cognitive decline [60, 61], being by far the most powerful predictor for the development of dementia in these population [62]. RBD in PD is also associated to an increased neuropsychiatric burden, since an increased prevalence of anxiety, depression, and

Table 1. Studies assessing the frequency of ICDs in PD-RBD+ compared to PD-RBD-

Study	PDRBD+ vs PDRBD-	RBD diagnosis	ICDs diagnosis	Results
Postuma et al. [54]	21 vs 15	VPSG	Clinical interview (no standard criteria)	No difference in single ICD frequency (no cumulative prevalence assessed)
Romenets et al. [76]	54 vs 44	VPSG	Clinical interview (no standard criteria)	No difference in single ICD frequency (no cumulative prevalence assessed)
Fantini et al. [71]	106 vs 110	Questionnaires (RBDSQ + RBD1Q)	Questionnaire (QUIP-Current-SF)	↑ ICDs symptoms in PD-RBD+ OR: 4.8
Kim et al. [73]	578 vs 366	Clinical interview	Midi	↑ in PD-RBD+ but no difference after adjusting for age and PD duration
Bayard et al. [74]	31 vs 67	VPSG	Clinical interview Standard criteria	No difference in ICD frequency
Rolinski et al. [75]	224 vs 251	Questionnaire (RBDSQ)	Questionnaire (QUIP-Current-SF)	↑ ICDs symptoms in PD-RBD+ (when RBDSQ cut-off ≥ 8)
Bellosta Diago et al. [72]	26 vs 47	Questionnaire (RBDSQ)	Questionnaire (QUIP-Current-SF)	↑ ICDs symptoms in PD-RBD+ QUIP score
Ramirez-Gomez et al. [77]	255 PD	Questionnaire (RBDSQ)	Questionnaire (QUIP-Current-SF)	↑ RBD in PD-ICD vs PD-noICDs (27% vs 12%) OR for ICDs 4.5
Fantini et al. [78]	80 PD (40 ICDs vs. 40 noICDs)	VPSG	Clinical interview standard criteria	↑ RBD in PD-ICD vs PD-noICDs (85% vs 52%) OR for RBD 4.9

RBD REM sleep behavior disorder, *ICDs* impulse control disorders, *VPSG* video-polysomnography, RBDSQ RBD Screening Questionnaire, RBD1Q *RBD* single question, *QUIP* Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease impulse control disorder have been reported in this population [63•].

Pathophysiology of RBD is thought to be caused by a dysfunction within the brainstem neuronal circuitry involved in motor control during REM sleep. In humans, the latter include the ventral mesopontine junction, the pedunculopontine nucleus, the laterodorsal tegmental nucleus, the locus coeruleus, and the peri-LC α area in the pons, and magnocellular, gigantocellular, and paramedian nucei in the medulla. The mechanisms of REM sleep generation and REM sleep atonia have been recently elucidated by the extensive work of Luppi et collaborators in rats. REM-on glutamatergic neurons localized in the caudal sublateral nucleus (the equivalent of peri-LC α) send excitatory projections to REM-on GABA/glycinergic premotoneurons localized in the ventral medullary reticular formation, namely the ventral and alpha gigantocellular nuclei and the nucleus raphe magnus. Those structures hyperpolarize the spinal motoneurons through direct inhibitory projections [64, 65]. Indeed, an animal model of TCSP was recently obtained from the knockout rats for the GABA receptors and glycine [66].

Pathological data on RBD are scarce and most data are available from neurodegenerative diseases-related RBD. Thus, inclusions of α-synuclein within Lewy bodies, the pathological hallmark of Parkinson's disease, and dementia with Lewy bodies (DLB), have been found in the pedunculo-pontine/laterodorsal tegmental nucleus or in the Locus Coeruleus of RBD patients [67], but their causal role on RBD is debated [68]. Furthermore, no difference was observed in the degree of neuronal loss or burden of α-synuclein pathology in a study assessing DLB patients with and without RBD [69].

In humans, most observed lesional cases of RBD were related to anatomical lesions at the brainstem level (vascular, tumoral etc.) [70]. However, cases of RBD occurring in concomitance with limbic lesions with a spared brainstem have been reported, suggesting a role of the limbic system in the pathophysiology of RBD, at least in those cases [71, 72]. Indeed, limbic system regulates emotions during wakefulness and is intensely activated during REM sleep, particularly the amygdala, probably in relationship to the emotional and motivational aspects of dreams [73]. Moreover, reciprocal strong anatomical connections link the amygdala to the pedunculo-pontine nucleus, a region modulating REM sleep atonia [74]. Finally, reward system, particularly the ventral tegmental area and the nucleus accumbens, is known to be highly activated during REM sleep [73]. Direct projections from the ventral tegmental area to the sublaterodorsal nucleus, a key area for REM sleep generation and REM sleep muscle atonia, have been described, suggesting a possible modulatory role of the reward system in REM sleep regulation [75].

The association between ICD and RBD

An association between ICDs and RBD in Parkinson's disease has been recently reported by our group and confirmed by most, although not by all, studies. Results of the investigations exploring this association are illustrated in Table 1. We first assessed the frequency of ICDs symptoms in a sample of 216 patients with PD with and without probable RBD (pRBD, i.e., assessed by questionnaire) [77]. A higher proportion of one or more ongoing ICD symptoms was reported in PD with pRBD (PDpRBD+) compared to PDpRBD− (53% vs 28%; $p = 0.0002$). In a multivariate regression analysis accounting for gender, age of onset, PD duration, PD severity, depression score, and total and dopaminergic agonist-LEDD, RBD was associated with a relative risk of 2.59 for any ICD symptom ($p = 0.001$). In particular, PDpRBD+ had a more than fourfold risk for symptoms of pathological gambling (relative risk [RR]: 4.87; $p = 0.049$) compared to PDpRBD−.

A similar study performed in a smaller sample of PD patients replicated these results [78]. However, other studies failed to observe this association. In a cohort of 944 PD patients, one study found an increased frequency of ICDs (assessed by a modified version of the Minnesota Impulsivity Disorders Inventory) in PD with pRBD compared to those without RBD, but the difference failed to reach significance after adjusting for age and disease duration [79]. On the other hand, the only study assessing ICDs in PD patients with and without videopolysomnographically(vPSG)-confirmed RBD failed to find an association between ICDs and RBD [80]. More recently, in a study assessing motor and non-motor features in a sample of 475 PD patients, participants with questionnaire-assessed RBD reported an increased frequency of punding (10.0% vs 4.0%, $p = 0.02$) and of dopamine dysregulation syndrome (7.8% vs 2.4%, $p = 0.01$) when using a more stringent cut-off that increased the specificity of the RBD screening questionnaire [81]. Finally, a Latin-American multicentric study, performed in a cohort of 255 PD patients, found that the history of REM sleep behavior disorder was associated to an increased risk to develop ICDs (OR = 4.37; 95% CI, 2.26–8.45) [82]. Differences between studies may be ascribed to methodological differences in assessing RBD and ICDs, insufficient power due to low number of patients with ICDs, and incomplete age- and sex- and severity-matching between groups. To overcome this concern, we performed a study aimed to assess the frequency of vPSG-confirmed RBD in 40 sex- and age-matched PD patients with current ICDs diagnosed according to standard criteria, compared to 40 PD patients without any history of ICDs [83•]. We observed that vPSG-documented RBD was more frequent in PD patients with ICDs compared to those without ICDs (85% vs. 53%, $p = 0.0001$). Furthermore, 3 out of the 6 patients with ICDs who failed to show REM sleep without atonia (RSWA) at vPSG did report a typical history of dream-enacting behaviors, with 2 of them showing brief REM sleep behavioral events (RBE) at vPSG, a condition that was recently shown to represent a "prodromal RBD" [84]. Thus, when pooling together patients with RBD and RBE, the cumulative frequency of RBD in patients with ICDs would raise 93%. Moreover, in a multivariate regression analysis including age of onset, PD duration and severity, treatment duration, levodopa- and dopamine agonists-equivalent daily doses and antidepressant use, RBD was still associated with ICDs in PD (odds ratio 4.9 [CI = 1.3;18.5], $p = 0.02$) [79].

Currently, no longitudinal studies are available in order to estimate the actual risk to develop ICDs over time in PD patients with and without RBD taking DRT. However, taken together, cross-sectional data suggest that PD-RBD may have an increased vulnerability to develop ICDs, compared to PD patients without RBD, probably due to a more severe impairment in the mesocorticolimbic pathway.

Risk factors for ICDs in PD populations are poorly defined, and the predicting value of each of them is largely unknown. Besides DRT and the presence of dyskinesia, no other features of PD appear to be so strongly associated with ICDs than RBD. Indeed, dyskinesia are more common in ICD patients than those without [44, 85], and the occurrence of early and severe dyskinesias (within the first 12–24 months) might be a warning sign for subsequent development of ICDS, particularly DDS [41]. Interestingly, an increased frequency of dyskinesia has also been observed in patients with PD with RBD [55•, 58], suggesting some shared disease-mediated neurobiological effects.

Finally, no study has assessed the frequency of ICD in iRBD, a condition that may precede by many years the development of an alpha-synucleinopathy and that is not treated with dopaminergic drugs. However, some studies reported an increased frequency of addictive behaviors in iRBD such as smoking, but not alcohol or caffeine use, compared to either control subjects or to a sample of PD patients [86, 87]. Actually, even if a substantial body of evidence indicates a lower frequency of addictive behaviors in PD (suggesting a potential protective role of smoking in the development of PD), an increased frequency of regular smokers was recently found in PD patients with RBD compared to those without RBD, in a cohort of 189 PD patients [88]. This may further support the notion of (early) behavioral changes associated with the "RBD phenotype."

Therapeutic strategies in PD patients with RBD

Detecting RBD in PD may represent a unique opportunity to identify those patients who are at higher risk to develop ICDs. This may be particularly relevant for the clinician, allowing him to set up preventive strategies and orienting his therapeutic choices. Indeed, screening for RBD may be crucial in de-novo patients, before initiating a DA therapy, especially in the youngest ones, since young age seems to be an additional risk factor for ICDs.[1] V-PSG represents the gold standard for the diagnosis of RBD. However, it is an expensive and time-consuming procedure requiring a specific expertise and is not always available in the clinical setting. Several screening questionnaires for RBD are available, including the RBD screening questionnaire (RBDSQ) which has been validated in PD population [89, 90], the RBD single question (RBD1Q) [91], the Hong Kong [92], and the Innsbruck questionnaires [76].

Non-ergoline dopaminergic agents are recommended in the treatment of PD in both the early and advanced stages. They include pramipexole and ropinirole on immediate or extended release formulations, as well as rotigotine on a transdermal delivery, all of them acting preferentially on D2/D3 dopamine receptors. While in the past years the use of DA agonists in early PD was the preferred management approach as a part of "levodopa sparing" strategy in order to delay motor complications, recent follow-up studies revealed no long-term advantages to initiate treatment with dopamine agonist or levodopa [93]. On the other hand, dopamine agonists, especially in their extended release formulation, have proven to be useful on non-motor symptoms, such as pain, anxiety, mood symptoms and sleep [94, 95].

In light of the strong association between D3/D2 agonists use and the emergence of ICD [11], it seems reasonable to recommend that dopaminergic agonist should be avoided in these patients, at least as a first line-therapy, or given at the lowest effective dose.

Whatever type of DRT, an increased surveillance of symptoms of ICDs and related behaviors should be highly recommended in PD patients with RBD. This implies educating patient and caregiver to recognize and report any early and benign changes in behavior potentially related to ICD, such as hobbyism, increased creativity, nighttime activities, and euphoric mood [96••].

In the event of ICD, the most effective way to alleviate this side effect is to taper or discontinue dopamine agonist therapy.[1] Yet, it is increasingly known that a subset of patients who taper DA may develop dopamine agonist withdrawal syndrome (DAWS). The latter consists in a severe, stereotyped cluster of physical and psychological symptoms that correlate with dopamine agonist withdrawal in a dose-dependent manner. It includes anxiety, panic, dysphoria, depression, pain, apathy, and anhedonia, which can be refractory to dopaminergic treatment. First retrospective studies have suggested the emergence of DAWS in about 14%–18% in PD after discontinuation of DA, while a recent prospective study found an even higher prevalence of DAWS, being observed in up to 24% of PD patients [97].

Actually, it has been shown that DAWS is particularly frequent in the context of ICDs, and that ICDs are virtually present in all DAWS-affected patients [98]. Furthermore, in the setting of ICDs, patients who are unable to discontinue dopamine agonist therapy may then experience chronic impulse control disorders [97]. Interestingly, it has been postulated that this subset of PD patients may present with a "mesolimbic variant" of PD, characterized by a more pronounced deficiency of mesocorticolimbic dopamine, underlining the increased vulnerability to both ICDs and DAWS [99].

On the other hand, an increased frequency of neuropsychiatric disorders, including impulse control disorders, but also apathy, anxiety, and depression, has been reported in patients with RBD associated to Parkinson's disease [62], pointing to a more severe dysfunction within the mesocorticolimbic circuitry in PD-RBD patients.

The risk of DAWS in PD patients with RBD has not been assessed yet; however, given their peculiar psychobehavioral profile encompassing mesocorticolimic dysfunctions, it is reasonable to hypothesize that PD-RBD patients might be at higher risk of DAWS.

Currently, there is no effective treatment for DAWS, and treatments for ICDs are very limited. Thus, early recognition of risk factors associated to both ICDs and DAWS is critical for preventing these devastating psychiatric manifestations. In particular, to advise patients about the risks of DAWS prior to the initiation of dopamine agonist therapy, and to follow patients closely for withdrawal symptoms during dopamine agonist taper, is highly recommended in PD with RBD. Gradual decrease of DA dosage could reduce the risk of DAWs, but this should be confirmed by specific studies.

To sum up, clinicians should be aware of the association between ICDs and RBD in PD and carefully check for symptoms of RBD prior to initiating a DRT. This may include performing a full in-lab nocturnal video-PSG recording, or use screening questionnaires when vPSG is not available. In the presence of either a v-PSG confirmed RBD or a typical history of this parasomnia, dopamine agonists should be avoided when possible, or given at the lowest effective dose. In case of ICDs, tapering of dopamine agonists should be gradual and symptoms of DAWS should be systematically checked. Increased surveillance of ICDs symptoms, implying a patient's and caregiver education to recognize early changes in behavior and in mood potentially related to a hyperdopaminergic status, should be also part of the preventive strategies.

Compliance with Ethical Standards

Conflict of Interest

Franck Durif reports other from Allergan, other from Aguettant, personal fees from Abbvie, grants from Abbott, other from medtronic, outside the submitted work. Maria Livia Fantini and Ana Marques each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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