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REVIEW ARTICLE

Dopamine Agonists and Impulse Control Disorders: A Complex Association

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Abstract Impulse control disorders (ICDs) are a well-known adverse effect of dopamine agonists (DAAs). This critical review aims to summarize data on the prevalence and factors associated with the development of an ICD simultaneous to DAA use. A search of two electronic databases was completed from inception to July 2017. The search terms were medical subject headings (MeSH) terms including "dopamine agonists" AND "disruptive disorders", "impulse control disorders", or "conduct disorders". Articles had to fulfill the following criteria to be included: (i) the target problem was an ICD; (ii) the medication was a dopaminergic drug; and (iii) the article was an original article. Of the potential 584 articles, 90 met the criteria for inclusion. DAAs were used in Parkinson's disease (PD), restless legs syndrome (RLS) or prolactinoma. The prevalence of ICDs ranged from 2.6 to 34.8% in PD patients, reaching higher rates in specific PD populations; a lower prevalence was found in RLS patients. We found only two studies about prolactinoma. The most robust findings relative to the factors associated with the development of an ICD included the type of DAA, the dosage, male gender, a younger age, a history of psychiatric symptoms, an earlier onset of disease, a longer disease duration, and motor complications in PD. This review suggests that DAA use is associated with an increased risk in the occurrence of an ICD, under the combined influence of various factors. Guidelines to help prevent and to treat ICDs when required do exist, although further studies are required to better identify patients with a predisposition.

Key Points

The use of dopamine agonists could contribute to the development of impulse control disorders (ICDs).

We need to consider ICDs as multifactorial disorders, involving drug-, patient-, and disease-related factors.

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1 Introduction

1.1 Dopamine and Dopaminergic Pathways in the Central Nervous System

Dopamine is a neurotransmitter that is particularly important as it is involved in both everyday brain functioning (such as the control of motor function, motivation, and reinforcement learning) and in several common disorders of brain functioning, notably Parkinson's disease (PD), drug dependence, and certain endocrine disorders [1].

Three main dopaminergic pathways are described in the central nervous system (CNS): (i) the nigrostriatal pathway consisting of cell bodies in the substantia nigra whose axons terminate in the corpus striatum; (ii) the mesocorticolimbic pathway (also known as the reward system), whose cell bodies are situated in the ventral tegmental area and whose axons project to parts of the limbic system, in particular the nucleus accumbens (NAcc) and the amygdaloid nucleus, and to the frontal cortex; and (iii) the tuberoinfundibular pathway, whose cell bodies are found in the ventral hypothalamus and project to the median eminence and pituitary gland [1]. The first pathway is particularly involved in motor function, while the second pathway is especially implicated in reward- and aversion-related cognition as well as executive functions. The third pathway influences the secretion of certain hormones, including prolactin. The impairment of these different pathways leads to a variety of disorders, ranging from important motor deficits (as is the case in PD) to the compulsive repetition of rewarding behavior (as is the case in addictive disorders and ICDs).

1.2 Dopamine Agonists

Dopamine agonists (DAAs) represent a pharmacological class of drugs that act on the nervous system. The following molecules are all DAAs: bromocriptine, pergolide, piribedil, lisuride, cabergoline, pramipexole, ropinirole, rotigotine, and apomorphine. The main indication of this class of drug is PD. Bromocriptine, pergolide, piribedil, and cabergoline exhibit a slight selectivity for dopamine $D_{2/3}$ over D_1 receptors. Lisuride acts specifically on D_2 receptors. The use of bromocriptine, pergolide, lisuride, and cabergoline, which are all ergot derivatives, is currently limited mainly due to their adverse effects. The aforementioned drugs have in fact been supplanted by pramipexole and ropinirole, which are $D_{2/3}$ selective and thus better tolerated [1]. These two drugs have a highly specific affinity to cerebral D_3 receptors, which are known to be localized to the mesolimbic system [2]. Rotigotine is a newer DAA, delivered via transdermal patch, which is highly selective to D_3 receptors as compared to D_2 receptors. Apomorphine, which has approximately equal affinities for D_2 and D_3 [3], is only active when administered via injection and has a short onset time and duration.

1.3 Parkinson's Disease, But Also Restless Legs Syndrome and Prolactinoma…

DAAs are mainly indicated to treat PD, although they are also used to relieve symptoms of restless legs syndrome (RLS) and prolactinoma or lactation inhibition. Others diseases may be anecdotally targeted by the prescription of DAAs, including fibromyalgia [4] and tetrahydrobiopterin deficiency [5], but use for these diseases falls outside of the approved recommendations.

1.4 Impulse Control Disorders (ICDs) Associated with Dopamine Agonists

When treating CNS disorders, it is often a desire to target a certain type of receptor; activating or inhibiting it in only a specific neuronal pathway. However, drug action is rarely limited to one region of the brain and a drug tends to impact a given receptor type throughout the brain [1]. The first cases of iatrogenic impulsive behaviors were reported in the early 2000s after DAAs received marketing authorization and began to be widely prescribed for PD [6, 7]. These first cases were considered to be iatrogenic based on chronological and pharmacological arguments: (i) they appeared after the onset of PD and dopamine replacement therapy (DRT) initiation and disappeared after discontinuing DRT; and (ii) DRT acted on dopamine receptors in both the nigrostriatal pathway and the reward pathway, which plays a role in addictive behavior. Several reviews have compiled published case reports or case series [8, 9] on this topic. Reported impulsive behaviors were pathological gambling, hypersexuality, compulsive shopping, binge eating, obsessive hobbying, punding, and compulsive medication use. The authors have rigorously examined the link between DRT and iatrogenic impulsive behaviors while considering a large range of disorders under a single umbrella term: impulse control disorders (ICDs) [10, 11]. ICDs are a heterogeneous group of diseases that are now included in the extended "Disruptive, Impulse Control, and Conduct Disorders" chapter in the *Diagnostic and Statistical Manuel of Mental Disorders, Fifth Edition* (DSM-5) [12]. ICDs involve dysfunctions in both emotional and behavioral regulation. A shared key symptom of all ICDs is the failure to resist an impulse or temptation to perform an act that is harmful to a person or to others [13]. Individuals experience an increased sense of tension prior to an act and pleasure, gratification, or the release of tension at the time of committing the act. Some disorders that are classified in other nosographic categories (binge eating disorder in "Feeding and Eating Disorders" or gambling disorder in "Substance-Related and Addictive Disorders") are considered in the literature in this field as ICDs due to their clinical proximity or evolutions in classifications. Similar adverse drug reactions have also been reported in RLS [14–23] and prolactinoma patients [24, 25], thus implying that nigrostriatal denervation is not a prerequisite for the development of ICD. However, only a minority of individuals with from PD, RLS, or prolactinoma develop ICDs. This is in contrast to the high frequency of the other adverse effects (i.e., nausea, low blood pressure, or

nightmares), which are directly linked to the central or peripheral action of DAAs. Concluding that medication is the only factor involved in the onset of ICDs would be simplistic and dangerous. Many other potential risk factors should be considered, including individual predisposition and/or disease-related factors.

1.5 Lack of Evidence

A substantial amount of literature is consecrated to the examination of the links between the use of DAAs in PD and the development of ICDs [2, 11, 13, 26–63], and this topic continues to be a very active field of research. In most cases, emphasis is placed on iatrogenic factors. Furthermore, the same association in RLS or prolactinoma is rarely addressed, and, to the best of our knowledge, there is no review available that takes into account the three diseases for which DAAs are prescribed. To fill this void, we undertook a comprehensive review of ICDs simultaneous to DAA use, integrating iatrogenic factors, predisposing factors, and disease-related factors. We decided to focus only on original articles based on a control study design. Finally, recommendations to manage ICDs are briefly provided.

2 Materials and Methods

A systematic review of available literature was conducted to identify all relevant publications pertaining to the links between the use of DAAs and ICDs. For this review, we complied with the Preferred Reporting Items for systematic reviews and Meta-Analyses (PRISMA) [64].

2.1 Search Resources

A search of two electronic databases was completed from inception to July 2017: PubMed and ScienceDirect. The search terms were medical subject headings (MeSH) terms including "Dopamine Agonists" AND "Disruptive, Impulse Control, and Conduct Disorders" found in the title, abstract, or keywords. Duplicates were eliminated. Additional records were included after manual search. The search strategy is summarized in Fig. 1.

2.2 Eligibility Criteria

Articles had to fulfill the following criteria to be included:

- The target problem was an impulse control disorder;
- The medication was a dopaminergic drug; and
- The article was an original article.

2.3 Article Selection

Firstly, articles were selected based on their titles and abstracts. Secondly, the full text of all of the included articles was read. Two of the authors (MGB and GCB) performed this work independently using the same bibliographic search. In the event of disagreement, the relevant articles were discussed.

2.4 Data Extraction

Clinical and pharmacological data were extracted from the articles (by MGB, YD, JL, MR, ET, NZ, and GCB). Factors taken into account included the sample size of the studies, the type of participants, the characteristics of the disease, the characteristics of the drug, the study design, and the objectives. The main results are presented in tables that summarize the prevalence data, the iatrogenic factors, the patient-related factors and the disease-related factors (Tables 1, 2, 3, 4 in Appendix).

3 Results

Ninety articles met the criteria for inclusion. DAAs were used in PD, RLS, or prolactinoma.

3.1 Prevalence

The results of the prevalence survey are presented in Table 1 in Appendix.

In PD patients, the prevalence of ICDs in general ranged from 2.6% [65] to 34.8% [66], reaching higher rates in specific populations: 39.1% in patients only treated using DAAs with a predefined minimum exposure to DAAs after study enrollment of at least 50 levodopa (L-dopa) equivalent daily dose (DAA-LEDD, calculated using the standard conversion factors described by Tomlinson and colleagues [67]) of DAA for at least 3 consecutive months [68] or 58.3% in early-onset PD (EOPD) patients [69]. No ICD stood out more than another, and authors reported discordant results concerning the frequency of each ICD.

In RLS patients, reported prevalences were lower, between 7.1% [70] and 11.4% [71]. Surprisingly, Bayard et al. [72] reported rates that were even lower for patients taking DAAs (2%) than for drug-free patients (2.5%), although DAA doses were three to five times lower in that study's RLS population than in other RLS populations.

We found only two studies about prolactinoma. ICDs were observed in two patients out of 20 in one study [73], and concerned a quarter of the sample in another [74].

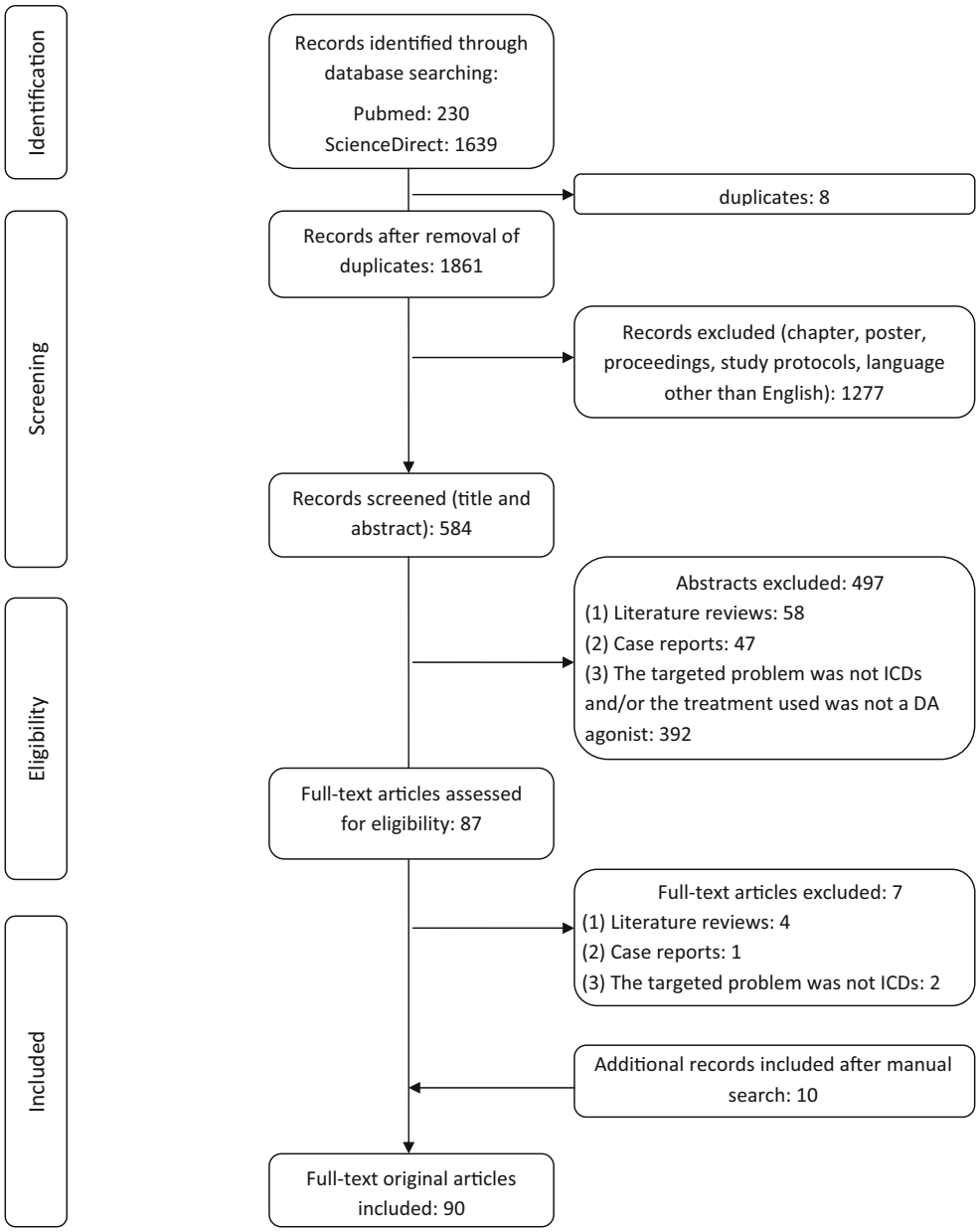

Fig. 1 Flow chart of the search

3.2 Drug-Related Factors

The results regarding drug-related factors are presented in Table 2 in Appendix.

Exposure to DRT was found to be a risk factor in the emergence of an adverse drug event such as ICD, and patients with ICDs were shown to take a significantly higher LEDD [75–83]. A study assessing PD patients treated with low dosages of DRT did not find any significant association between drug-related factors and ICDs after multivariate analysis [86].

3.2.1 Type of Dopamine Agonist (DAA)

Both DAA and L-dopa use was implicated in the development of ICDs in PD patients, although the odds ratio (OR) was nearly twice as high for DAAs [84]. According to numerous studies, DAA use is an independent predictor for developing an ICD in PD patients [75, 78, 83–96]. The six US Food and Drug Administration (FDA)-approved DAAs (pramipexole, ropinirole, cabergoline, bromocriptine, rotigotine, and apomorphine) had a strong signal, the strongest being pramipexole and ropinirole, which both

have a preferential affinity for D_3 receptors [91]. Several studies highlighted a potentially causal role of pramipexole [85, 90]. However, other studies did not conclude that there were any significant associations with respect to a specific DAA [68, 86, 97].

3.2.2 Dose of DAA

For many authors, exposure to a higher daily dose of DAA [70, 77, 81, 86, 90, 93, 98, 99] and a higher peak DAA dose [68] were significantly associated with the development of ICDs. Only a few studies did not find any association with dosage [80, 100, 101]. Two studies assessed the dose–response relationship. Lee et al. [102] reported a DAA dose–response relationship with compulsive shopping, gambling, and hypersexuality, and Perez-Lloret et al. [103] noted a non-linear dose–response relationship between DAAs and the frequency of ICD symptoms. Finally, a longitudinal study showed a recovery from compulsive behaviors after reducing the dosage of DAAs in 16 patients out of 22 [104].

3.2.3 Duration of DAA Treatment

It is difficult to draw conclusions on the link between DAA treatment duration and ICDs. For some authors, DAA treatment duration seemed to have an influence, with a longer duration being associated with the development of ICDs [105, 106], while for other authors DAA treatment duration was non-significant [68]. In long-term studies of rotigotine transdermal patches, the incidence of ICDs was relatively low during the first 30 months of exposure and higher over the next 30 months [107].

3.2.4 DAA Formulation

Most studies did not indicate the drug formulations employed. Yet, some recent publications have discussed the relevance of extended formulations. Todorova et al. [108] thus demonstrated that infusion therapies (apomorphine infusion and intrajejunal L-dopa infusion) were associated with the resolution or attenuation of pre-existing ICDs. ICDs could, however, develop after apomorphine infusion initiation, but the rate remained lower than that reported for oral short-acting DAAs [108]. Transdermal patches of rotigotine provide continuous drug delivery with a stable plasma concentration over 24 h. It is suggested that extended formulations limit ICD development compared with immediate-release (IR) formulations. Nevertheless, ICDs were reported as an adverse drug reaction in rotigotine long-term treatment [107].

3.2.5 Biological Aspects

From a neurobiological point of view, DAA use implies a modification of the neuronal signaling of reward expectation (mesolimbic dopaminergic hyperactivation), resulting in a sensitization towards ICDs [109]. DAAs may abate negative reinforcement in feedback-based learning [110]. A case-control study showed a significant DAA-induced reduction of neuronal activity in brain areas that are implicated in impulse control and response inhibition (lateral orbitofrontal cortex, rostral cingulated zone, amygdala, and external pallidum) in PD patients with DAA-induced pathological gambling compared with that of PD controls [111]. Furthermore, when using different forms of decision-making tasks, including delay-discounting tasks, DAA use was associated with greater choice impulsivity [79, 112], shorter reaction time [112, 113], and increased risk-taking [114, 115] in PD patients with ICDs compared with PD controls. Exogenous dopamine influences impulsive decision-making, which may precipitate the development of ICDs [79]. In PD patients with hypersexuality, DAA use results in an increased sexual desire after exposure to sexual content compared with non-medicated PD patients [89].

In RLS patients, the underlying neurobiology remains less clear. Bayard et al. [72] observed reduced decision-making capacity where outcome probabilities were unknown, although no difference was observed between drug-free and DAA-treated patients [72]. It is important to note that DAA doses were three to five times lower in this study population than in other RLS populations.

3.3 Patient-Related Factors

The results relating to patient-related factors are presented in Table 3 in Appendix.

3.3.1 Sociodemographic Characteristics

3.3.1.1 Gender Male gender was commonly found as an independent predictor for developing ICDs [66, 77, 78, 97, 105, 116, 117] as well as for pathological gambling or hypersexuality [102] in PD patients and in prolactinoma patients [74]. In contrast, female gender was

associated with the resolution of ICDs in PD patients during follow-up [100]. Female gender was found to be more frequent in RLS patients with ICDs [70].

3.3.1.2 Age A younger age [77, 80, 82, 84, 87, 92, 96, 97, 117–119] and an age under 65 years [66] or 68 years [103] were also commonly found to be independent predictors for developing an ICD. PD patients with pathological gambling were distinguished from PD with ICDs not otherwise specified and from PD controls of a younger age [82].

3.3.1.3 Other Sociodemographic Characteristics According to Weintraub et al. [84], PD patients with ICDs were most likely unmarried and living in the USA.

3.3.2 Co-Morbidities

3.3.2.1 Psychiatric Symptoms Mental illness was found to be significantly correlated to the presence of an ICD [120], except in one study [87]. Depression and anxiety were the highest-ranking correlates. A history of depression [99], symptoms of depression [85, 121], and a higher score of depression [66, 80, 82, 95, 122] were found to be predictors of the development of an ICD in patients with PD or RLS [123]. In a longitudinal study, Joutsa et al. [100] showed that the development of a novel ICD was associated with the concurrent increase in depression score. Conversely, one study reported only discrete symptoms of disinhibition [85]. A history of anxiety [99], trait anxiety [94], symptoms of anxiety or stress [123], and a higher anxiety score [76, 81, 82, 122] were also found to be predictors of the development of an ICD. Interestingly, a higher obsessive–compulsive score was reported in only one study [122]. PD patients with pathological gambling were distinguished from PD with ICDs not otherwise specified and from PD controls with a higher severity of psychotic symptoms [82].

3.3.2.2 Addictive Disorders In some studies, no link was found between addictive disorders and the development of an ICD [68, 87]. For others, substance use (and not a substance use disorder) of caffeine [68, 121], nicotine [68, 84, 90], stimulants (tea, mate) [96], alcohol [88], or drugs [70], as well as gambling practice [120] was found to be associated with ICDs. A family history of pathological gambling was reported in two studies [70, 84].

3.3.2.3 Sleep Problems More sleep problems were reported in patients with RLS [123] or PD [82, 96] with compulsions or ICDs.

3.3.2.4 Personality Predictably, the most assessed personality dimension was impulsivity, with authors reporting higher impulsivity scores [94, 122] and greater choice impulsivity [122]. PD patients with ICDs also made errors in perceptual decision-making tasks. Clinically, this implies that PD patients with ICDs may make disadvantageous decisions as they are often 'in a rush' to decide [113]. Similarly, a higher score of novelty-seeking [81] was found to be associated with ICDs, especially among PD patients with compulsive sexual behavior [122].

PD patients with ICDs were described as individuals with ineffective coping skills [120], a higher level of neuroticism and lower levels of agreeableness and conscientiousness [80], especially among PD patients with PG [121] or compulsive sexual behaviors [81]. EOPD patients with ICD symptoms scored higher on both self-assertive/antisocial and reserved/schizoid personality styles [121]. For their part, PD patients with pathological gambling displayed higher scores of bizarre ideation and cynicism than those without pathological gambling or ICD [124]. Finally, somatization appeared to be higher in patients with EOPD with ICD symptoms [121].

3.3.3 Biological Aspects

DRD3 p.Ser9Gly (rs6280) heterozygous variant CT genotype was found to be a predictor of ICDs among PD patients [83]. Another genotyping study also indicated a significant association with tryptophan hydroxylase type 2 (TPH2) (recessive) and dopamine transporter (DAT) gene variants (dominant) in PD patients with ICD or dopamine dysregulation syndrome (DDS), all the more so when the severity of the ICD or DDS was high [125]. TPH2 genotype was the strongest predictor of non-remission during follow-up. Finally, variants of *DRD1* rs4867798, *DRD1* rs4532, *DRD2/ANKK1* rs1800497, and *GRIN2B* rs7301328 were found to be associated with an increased risk of developing impulse control behaviors among PD patients [126]. Kraemmer et al. [127] found heritability of ICD behavior to be 57%, *OPRK1*, *HTR2A*, and *DDC* genotypes being the strongest genetic predictive factors.

An imaging study based on single photon emission computed tomography (SPECT) of the DAT concluded that the DAT density differed in PD patients with PG compared with PD patients without ICD or healthy controls. PD patients with PG showed a reduced tracer binding in the right ventral striatum, possibly reflecting either a reduction of mesolimbic projections or a lower membrane DAT expression on presynaptic terminals [128]. A recent study suggested that changes in DAT availability over time increased the risk of incident ICDs [129].

Another SPECT study showed a reduction of left putaminal and left inferior frontal gyrus tracer uptake in PD patients with ICDs compared with those without ICD [130]. This frontostriatal dysconnectivity may be related to a DA and serotonin network dysfunction centered around the left putamen, supporting the idea of a monoaminergic frontostriatal disconnection syndrome as the biological basis of ICD symptoms in PD. This may reflect either a pre-existing neuronal trait vulnerability for impulsivity or the expression of a maladaptive synaptic plasticity under non-physiological dopaminergic stimulation [130].

D_2 receptor availability was no different between PD patients with or without ICDs at baseline, but a greater reduction of ventral striatum ^{11}C-raclopride binding potential following L-dopa challenge with reward-related cue exposure relative to neutral cue exposure was observed [131]. PD patients with pathological gambling seemed to have dysfunctional activation of DA autoreceptors in the midbrain and low DA tone in the anterior cingulate [132]. A recent study failed to demonstrate any D_3 upregulation in PD patients with ICD [133].

Finally, an imaging study showed that PD patients with ICD, compared with those without ICD and healthy controls, had a thicker cortex in the anterior cingulate and the orbitofrontal cortex, which are cortical areas linked to impulsivity and inhibition behaviors [134]. These structural abnormalities were correlated with the severity of the ICD.

3.4 Disease-Related Factors

A summary of the results relating to disease-related factors is presented in Table 4 in Appendix.

3.4.1 Age of Onset

Most studies concluded that a younger age at PD onset was an independent predictor for developing an ICD in PD patients [76–78, 80, 82, 94, 99, 102, 105, 106, 118, 135]—especially when the ICD was pathological gambling [82]—or in RLS patients [70]. Recently, Krishnamoorthy et al. [83] emphasized a limit of 50 years and under in PD patients with ICDs.

3.4.2 Disease Duration

Similarly, a longer PD duration was found to be a factor [80, 82, 102, 137], except in a few cases [68, 85]. Rana et al. [78] identified stages 1–2 of PD as one of the five common variables among patients who developed ICDs.

3.4.3 Type of Disease

Compared with PD patients without ICDs, those with ICDs displayed a higher frequency of motor complications [68, 80, 102], with greater motor disease complexity [76] and motor fluctuations [93]. Conversely, PD patients with motor complications were more likely to have an ICD [75]. Furthermore, a higher score on the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part 1 was found in two studies [93, 94], as well as increased functional impairment, decreased motivation [122] and a higher Mini-Mental State Examination (MMSE) score [68]. Finally, patients with right-onset PD exhibited significantly higher levels of novelty-seeking than the patients with left-onset PD, which may increase the risk of developing an ICD when associated with the simultaneous use of DAAs [138]. However, Pontone et al. [85] and later Kenangil et al. [101] found no significant association between PD features and the presence of ICD, and Ramirez Gómez et al. [96] found a negative association between motor fluctuations or dyskinesias and ICDs.

3.4.4 Biological Aspects

To disentangle the effects of the disease process and DA medication and the development of ICDs, Al-Khaled et al. [139] compared medicated and unmedicated PD patients, RLS patients and healthy controls. Using a delay discounting task, they demonstrated that unmedicated PD patients had a higher discounting rate. Thus, impulsive decision-making in PD patients may not be a side effect of dopaminergic treatment but rather a trait marker of PD. These results were in accordance with those of Aarts et al. [140], who demonstrated the aberrant impact of rewards in PD, a reflection of reward-related impulsivity, was directly related to the degree of dopamine neuron loss, i.e., to a factor intrinsically related to the disease pathology itself.

4 Discussion

4.1 Main Findings

Through our review, we have shown that this topic has been extensively studied over the last 10 years, allowing for us to obtain prevalence results from large samples. Publications mostly focused on iatrogenic factors, and progressively extended to patient- and disease-related factors. All this illustrates the complexity of this type of adverse drug reaction and the need to consider ICDs as multifactorial disorders. As recently noted by Voon et al. [141], ICDs reflect the interactions of the DRT with an individual's susceptibility, and the underlying neurobiology of PD. The most robust findings, supported by several studies, include the type of DAA (having a higher selectivity for D_3 receptors), dosage (higher daily dose), male gender (for PD), a younger age (although DAAs are more likely to be prescribed for younger PD patients), a history of depression and anxiety symptoms, an earlier onset of disease (it represents the same selection bias as for a younger age), a longer disease duration (for PD), and motor complications (for PD).

4.2 Limitations

The value of the results, however, is limited by several aspects. Firstly, it is important to note that the assessment of ICDs was to a great extent heterogeneous, based on standardized clinical interviews, self-report questionnaires, medical records, and caregiver reports. Assessments were not always based on validated tools or consensual diagnostic criteria, with an explored period that was not always specified. Sometimes, the authors reported subclinical disorders, at other times only symptoms. On other occasions, they referred to lifetime or current disorders. This heterogeneity can be seen in the number of terms employed to describe ICDs: overeating, binge eating disorder, bulimia, compulsive shopping or buying, compulsive sexual behavior, hypersexuality, gambling, excessive gambling, problem gambling, pathological gambling, compulsive behavior, impulsive and compulsive behavior, impulse control disorder, ICD–not otherwise specified, impulsive control and repetitive behavior disorder, repetitive behavior disorder, etc. Although the inclusion of excessive behaviors among ICDs (for instance, overeating) may seem surprising, one must remembered that all display a high level of impulsivity. In this respect, they are in fact quite similar to disorders that are included in the other nosographic categories (i.e., 'Feeding and Eating Disorders' and 'Substance-related and Addictive Disorders'). The prevalence of ICDS in patients using DAAs varies widely according to which assessment tool is used. It should be noted that the true frequency may be underestimated due to patients' lack of insight into ICDs or their hesitation to acknowledge an ICD out of shame or embarrassment [26].

Secondly, a large amount of heterogeneous data were collected on drugs, individuals, and underlying disease characteristics. However, the evaluation of certain factors, such as social determinants, was almost systematically neglected. Studies were not reproducible, making it difficult to draw general conclusions on the respective influence of each characteristic on the development of ICDs; this is especially true for psychological characteristics. Indeed, different studies evaluated different psychological dimensions, using different assessment tools. Poor decision-making and impulsivity are two dimensions regularly cited to influence ICD development. The challenge of differentiating between pre-existing personality traits, the impact of underlying disease, or the effects of DRT remains. A recent study demonstrated that exposure to pramipexole in PD patients without ICDs was associated with an increase in impulsive choices, acting essentially on decision-making processes [142]. The authors speculated that, in PD patients without ICDs, pramipexole could modulate the top–down control, which is generally impaired in PD patients with ICDs. In healthy controls, pramipexole was shown to increase the activity of the NAcc, enhancing the interaction between the NAcc and the prefrontal cortex [99]. It was suggested that pramipexole may exaggerate incentive and affective response to possible rewards, but reduce the top–down control of impulses. Furthermore, increased impulsivity may not only be dependent on medication but also on neuroanatomical abnormalities intrinsic to PD, with gray matter atrophy in impulse-control regions [143].

Thirdly, we lack information relative to the drug formulations used in all trials. Indeed, extended-release (ER) forms of DAAs were progressively introduced, and several randomized controlled trials have compared their safety with immediate-release (IR) forms in the past few years. For instance, according to the review by Fishman [144], the prevalence of ICDs is similar in both the IR and the ER forms of pramipexole. However, according to Stocchi et al. [145], the relative recent marketing of the new ER DAAs has not yet resulted in conclusive data on the incidence of ICDs during their use. Thus, transdermal ragotidine and ER pramipexole may have a safer profile than IR pramipexole and IR/ER

ropinirole [146]. ER forms provide a better stability of plasmatic drug concentrations. Pharmacokinetic factors (rate of onset, half-life) are thought to be a critical determinant of the reinforcing effects and abuse potential of a drug. Some authors consider ICDs as additive disorders, even if only gambling disorder has been included in the "Substance-Related and Addictive Disorders" chapter in DSM-5 [12]. We may assume that pharmacokinetic parameters could be involved, at least partly, in the development of ICDs. This is consistent with the fact that more ICDs have been described with DAA than with L-dopa, which is a prodrug needing a biotransformation to become an agonist (corresponding to an ER-like form). It is hypothesized that the acute release of DA in the ventral striatum in relation to a pulsed therapy could underlie the development of ICDs [108].

Fourthly, most of the studies were cross-sectional, which is not an optimal strategy for the observation of personality traits or psychiatric co-morbidities and for determining whether or not they are predisposing factors or rather a consequence of an adverse drug reaction or the underlying disease. Nevertheless, two studies conducted in drug-naïve PD patients compared with healthy controls concluded that PD itself did not seem to confer an increased risk of development of an ICD [147, 148].

Fifthly, some authors conducted multiple comparisons without applying corrections or using multivariate analysis and concluded several significant associations irrespective of the risk of the type I error.

Finally, the MeSH term "Dopamine Agonists" used for this review did not include partial DAA drugs that are also known to cause ICDs, such as aripiprazole [9, 149] and flupentixole [150].

4.3 Recommendations

Recommendations are based on two key principles: the prevention of ICDs and the treatment of ICDs when they occur. Several studies were recently published that provide guidelines for the management of ICDs in PD patients [45, 51, 151]. Part of these recommendations could also be used to address RLS or prolactinoma.

4.3.1 "Prevention is Better than Cure": How to Achieve 'P4 Medicine'?

'P4 medicine' can be achieved by adhering to the following recommendations:

- By encouraging a more systematic comprehensive assessment of patients to help in identifying those who are at risk of developing an ICD, sustained by the concept of *predictive* medicine;
- By better adapting the treatment strategy (avoiding drugs that are the most selective of D_3 receptors in patients who are at greatest risk), sustained by the concept of *personalized* medicine;
- By providing full and clear information on these potential adverse drug reactions to patients and by raising awareness of the risk among caregivers, to promote early detection and medical intervention, sustained by the concept of *participatory* medicine;
- By preferring the prescription of ER formulations that have proven to be non-inferior to the IR formulations, and are better tolerated, and by routinely monitoring the patients, sustained by the concept of *preventive* medicine.

4.3.2 When an ICD Occurs, it is Not Too Late

The priority is to stop or to control excessive behavior, with the objective of harm minimization. The first stage aims at optimizing the DA treatment by:

- Reducing the L-dopa equivalent daily dose or discontinuing the DAA [104], but with the risk of motor function deterioration and the occurrence of DAA withdrawal syndrome;
- Switching from one DAA to another that is less selective of the D_3 receptors [3, 27];
- Combining oral DAA at a lower dose with apomorphine [27] or orally disintegrating selegiline, which is a selective inhibitor of the monoamine oxydase type B [152].

The second stage is to propose non-pharmacological approaches, especially cognitive and behavioral therapy (CBT) focusing on ICD [153]. This implies promoting links between neurologists and psychiatrists and tailoring CBT to the particular characteristics of these patients in order to decrease the risk of relapse and dropout during treatment [153].

In the event of a negative outcome, the third stage involves less conventional treatment options:

- Bilateral subthalamic nucleus (STN) deep-brain stimulation (DBS): case reports have shown an

improvement after DBS [154], but a recent review provided inconsistent results [155].

– Specific pharmacological treatment of ICDs: several molecules were tested in a (very) small number of PD patients with ICDs. Antiepileptic drugs, such as topiramate [156], valproate [157], or zonisamide [158], and anti-craving drugs, such as naltrexone [159], could be effective therapeutic options, whereas antidepressant drugs, such as serotonin reuptake inhibitors [160], or atypical antipsychotics, such as quetiapine [161] or risperidone [6], were met with mixed results. Clozapine was tested with encouraging results in a few patients [162], but one must keep in mind its serious adverse effects and consider risks versus benefits for patients on an individual level.

5 Conclusion and Future Directions

The prevalence of ICDs ranged from 2.6 to 34.8% in PD patients, and from 7.1 to 11.4% in RLS patients. There are insufficient data available on prolactinoma to draw a conclusion with respect to prevalence. This review suggests that DAA use is associated with an increased risk in the occurrence of ICDs, under the combined influence of various factors. The most robust findings include the type of DAA (having a higher selectivity for D_3 receptors), dosage (higher daily dose), male gender (for PD), a younger age (although DAAs are more likely to be prescribed in younger PD patients), a history of depression and anxiety symptoms, an earlier onset of disease (this pertains to the same selection bias as younger PD patients), a longer disease duration (for PD), and motor complications (for PD). Recently, a new clinical–genetic prediction model that has reached high accuracy was proposed [127]. Guidelines to help in the prevention of ICDs and in their treatment when required do exist. Thus, identifying who is at risk of developing an ICD is crucial. Progress is still to be made to improve the evaluation of individual patients, using validated and consensual assessment tools, and by also integrating social factors. Further longitudinal studies including patients who have not yet developed an ICD would be useful in determining premorbid risk factors. Conducting literature-based meta-analysis, although difficult to achieve due to the heterogeneity of the data collected, could provide insight into the relative importance of the associated factors. Finally, large samples are needed to better characterize subtypes of patients with co-morbid ICD because beyond the associated factors reported in our review, it appears that they do not constitute a homogeneous group. This clinical intuition is well-supported by empirical evidence suggesting different evolutions after reduction or discontinuation of the DAA alleged to have cause the ICD. For some patients, DAA reduction or discontinuation is sufficient to obtain complete resolution of the ICD, while for others it is necessary to associate other measures. In the first case, one can imagine that the development of an ICD is a 'real' adverse drug reaction, linked to a particular sensitivity to DAAs, and which may be reversible by reducing DDA dosage under a specific threshold for each patient. In the second case, there may also be an addictive vulnerability involving biological, psychological, and environmental factors. DAA use would then only act as a catalyst, with the ICD finally evolving on its own. In these cases, the ICD also requires specialized addiction care.

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Compliance with Ethical Standards

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Appendix

Table 1 Prevalence survey

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Pontone et al. [85]	2006	100	PD patients (PD + ICD: 9 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 44.3 (±9) vs. 48.6 (±9) Mean duration (years): 4.6 (±62.2) vs. 6.2 (±5.5)	Pramipexole, ropinirole, amantadine, entacapone, selegiline, L-dopa *PD + ICD vs. PD–ICD:* L-dopa dose = 627 (±281) vs. 520 (±450) mg	Cross-sectional	To determine the frequency of ICDs	Prevalence = 9% ($n = 9$) ICDs: gambling (4%) = sexuality (4%) > spending (3%)
Grosset et al. [98]	2006	388	PD patients	PD	Pramipexole, ropinirole, pergolide, L-dopa, amantadine, entacapone, selegiline, anticholinergic.	Cross-sectional	To determine the frequency of excessive gambling	Prevalence = 4.4% ($n = 17$)
Weintraub et al. [86]	2006	272	PD patients	PD	Pramipexole, ropinirole, pergolide, L-dopa, amantadine	Cross-sectional	To determine the frequency of ICDs	Prevalence = 6.6% (at some point during the course of PD) and 4% (currently) ICDs: sexuality and gambling
Voon et al. [10]	2006	297	PD patients (PD + ICD: 30 patients, PD–ICD: 277 patients)	PD *PD + PG vs. PD + HS vs. PD + CS vs. PD–ICD:* Mean age at onset (years): 49 (±7) vs. 46 (±8) vs. 36 (±6) vs. 58 (±9)	L-Dopa, DAA, pramipexole, ropinirole.	Cross-sectional Case-control	To determine the frequency of HS and CS	*Prevalence:* HS: 2.4% (lifetime)/2.0% (current) CS: 0.7% (current)
Driver-Dunckley et al. [71]	2007	99	77 patients under DRT (current or past)	Idiopathic RLS Mean duration: 24 years (±18)	Pramipexole, ropinirole, pergolide, L-dopa, bromocriptine	Cross-sectional	To determine the frequency of gambling or other abnormal behaviors	Prevalence = 11.4% (8 patients out of 70 who completed the questionnaire) Change in gambling (7%) and in sexual desire (5%) after the use of DRT

Table 1 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Giladi et al. [105]	2007	383	193 PD patients (PD + ICD: 27 patients; PD − ICD: 166 patients) 190 age- and gender-matched HC	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 51.5 (±12.2) vs. 58.7 (±12.1) Mean duration (years): 10.3 (±4.9) vs. 9.7 (±6.6)	Ropinirole, pergolide, cabergoline, apomorphine, amandatine, selegiline, entacapone	Cross-sectional	To determine the frequency of ICDs	Prevalence = 14% (n = 27) ICDs: sexuality (8.8%) > eating (3.6%) > gambling (3.1%) = shopping (3.1%)
Crockford et al. [87]	2008	140	No demented-patients, with moderate to severe PD	PD	Pramipexole, ropinirole, pergolide, bromocriptine, L-dopa LEDD = 707 (±402) mg	Cross-sectional	To assess the prevalence of problem and PG	Prevalence = 9.3% (vs. 1.3% in general population)
Fan et al. [88]	2009	444	312 PD patients (PD + ICD: 11 patients; PD–ICD: 301 patients) 132 controls (spouses/caregivers of the patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 58.7 (±6.7) vs. 60.1 (±10.6) Mean duration (years): 5.3 (±2.5) vs. 5.7 (±2.9)	L-Dopa, piribedil, pramipexole, amantadine, pergolide, ergocriptine, bromocriptine *PD + ICD vs. PD–ICD:* Total LEDD = 487 (±289) vs. 392 (±224) mg	Cross-sectional	To determine the frequency of ICDs	Prevalence = 3.5% (n = 11, lifetime or current)
Bostwick et al. [65]	2009	267	PD regional patients (to reduce the referral bias)	PD	DAAs (24.7%), with only 14.2% in the therapeutic range Carbidopa/L-dopa (88.6%) without a DAA	Retrospective (medical records, excluding those in which the behavior predated the PD onset)	To determine the frequency of compulsive gambling and HS	Prevalence = 2.6% (n = 7), but 18.4% of patients taking a DAA at therapeutic doses All cases were taking a DAA (either pramipexole or ropinirole), at therapeutic doses, but no case was taking carbidopa/L-dopa or a DAA at subtherapeutic doses

Table 1 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Pallanti et al. [163]	2010	24	24 PD patients who underwent STN DBS	PD	STN DBS	Cross-sectional Patient- and relative-completed survey	To determine the frequency of punding	Prevalence = 20.8% (n = 5)
Weintraub et al. [84]	2010	3090		PD	DAAs and/or L-dopa (n = 3031) *DAAs (mean daily dosage and LEDDs):* Pramipexole: 3.1 mg (SD = 1.7) and 306.9 mg (SD = 168.2); Ropinirole: 11.1 mg (SD = 6.6) and 277.9 mg (SD = 164.9); Pergolide: 2.9 mg (SD = 1.7) and 286.6 mg (SD = 169.3)	Cross-sectional Case-control (matching on age, sex and DAA treatment) *(DOMINION study)*	To determine the frequency of ICDs	Prevalence = 13.6% (3.9% with ≥ 2 ICDs) ICDs: shopping (5.7%) > gambling (5%) > eating (4.3%) > sexuality (3.5%)
Lee et al. [102]	2010	1167	PG patients	PD Mean age at onset (years): 58 (±11) Mean duration (years): 7 (±4)	Stable DRT for at least 3 months Mean duration of DRT: 5.0 years (± 3.8)	Cross-sectional	To determine the frequency of ICRBs	Prevalence = 10.1% ICRBs: punding (4.2%) > eating (3.4%) > sexuality (2.8%) > shopping (2.5%) > gambling (1.3%)
Kenangil et al. [101]	2010	554	PD patients (PD + ICD: 33 patients; PD − ICD: 65 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 49 (±9) vs. 52 (±11) Mean duration (years): 8 (±5) vs. 7 (±5)	Pergolide, cabergoline, pramipexole, ropinirole, piribedil, lisuride *PD + ICD vs. PD-ICD:* DAA-LEDD = 369 (±181) vs. 319 (±208) mg Total LEDD = 702 (±2369) vs. 640 (±357) mg	Cross-sectional	To determine the frequency of ICDs	Prevalence = 5.9% ICDs: punding (57%) > sexuality (42%) > eating (27%) > shopping (24%)

Table 1 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Pourcher et al. [123]	2010	97	97 RLS patients: 32 untreated patients without compulsions 53 DAA-treated patients without compulsions 12 DAA-treated patients with compulsions	RLS	Stable DAA (average dose 0.52 mg pramipexole equivalent)	Longitudinal T1: baseline T2: 4 months T3: 8 months	To determine the frequency of motor/behavioral compulsions	Prevalence = 12.4% (n = 12, development of a new compulsion) Compulsions: eating (n = 4) > shopping (n = 3) > trichotillomania = tic-like phenomena (n = 2) > gambling (n = 1)
Hassan et al. [106]	2011	321	DAAs-treated PD patients	PD	Ropinirole and pramipexole, L-dopa, selegiline, rasagiline, amantadine, entacapone	Cohort (retrospective)	To determine the frequency of compulsive behaviors	Prevalence = 16% Compulsive behaviors: gambling > sexuality > shopping > eating > hobbying > computer use
Martinkova et al. [73]	2011	20	20 patients with pituitary adenomas (mostly prolactinomas) taking DAAs	Pituitary adenomas	Cabergoline, bromocriptine, and quinagolide	Cross-sectional	To determine the frequency of ICDs	Prevalence = 2/20 patients ICDs: sexuality (n = 1) and gambling and eating (n = 1)
Auyeung et al. [136]	2011	213	PD patients (PD + ICD: 198 patients; PD–ICD: 15 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 45.7 (±5.6) vs. 59 (±10.8) years Mean duration: 13.5 (±5.6) vs. 8.9 (±4.8) years	Bromocriptine, ropinirole, pramipexole, rotigotine, L-dopa *PD + ICD vs. PD–ICD:* Dose of DAA-LEDD = 277 (±147) vs. 85 (±98) mg Total LEDD = 1215 (±635) vs. 634 (±330) mg	Cross-sectional	To determine the frequency of ICDs	Prevalence = 7%

Table 1 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Zahodne et al. [164]	2011	96	96 PD patients (PD + BED: 9 patients; PD–BED: 87 patients)	PD *PD + BED vs. PD–BED:* Mean age at onset (years): 58 (±8) vs. 56 (±13) Mean duration (months): 124 (±57) vs. 120 (±109)	DAA STN DBS surgery	Cross-sectional	To determine the frequency of ICDs, in particular BED and subthreshold BED	Prevalence of BED = 1% (8.3% for subthreshold BED) Other ICDs: gambling (17.8%) > shopping (11.5%) > hoarding (8.3%) > sexuality (1%)
Voon et al. [70]	2011	140		RLS	DAAs (ropinirole 2–4.5 mg/day: $n = 3$; pramipexole 0.72–1.4 mg/day: $n = 3$; lisuride 2.5 mg/day: $n = 1$; cabergoline 3 mg/day: $n = 1$) L-dopa (100 mg/day: $n = 3$)	Cross-sectional	To determine the frequency of ICDs	Prevalence = 7.1% RLS + ICD ($N = 10$): Medication: DAAs ($n = 7$) > L-dopa ($n = 2$) > DAA + L-dopa ($n = 1$) ICDs: eating ($n = 6$) > shopping ($n = 5$) > gambling or punding ($n = 3$) > sexuality ($n = 2$)
Lim et al. [137]	2011	200	PD patients	PD	Piribedil, pramipexole, ropinirole, bromocriptine, amantadine Low dosages of DRT	Cross-sectional	To determine the frequency of ICDs and subsyndromal ICBs	Prevalence any ICD = 23.5% ICDs: eating (13.5%) > sexuality (13.0%) > shopping (6%) > gambling (3.5%) Prevalence any ICB = 35% ICBs: punding or hobbyism (20%) > compulsive medication use (4.5%)

Table 1 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Limotai et al. [77]	2012	1040	PD patients, excluding those who were never exposed to DAA (PD + ICD: 89 patients; PD–ICD: 951 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 52 (±10) vs. 59.7 (±12) years Mean duration: 11.5 (±6.1) vs. 11.3 (±6.8) years	*PD + ICD vs. PD–ICD:* LEDD = 971 (±663) vs. 672 (±512) mg DAA-LEDD = 292 (±184) vs. 142 (±176) mg Total LEDD = 1122 (±644) vs. 779 (±543) mg	Retrospective (cohort)	To determine the frequency of DAWS, DDS and ICDs	Prevalence of ICDs = 8.6%
Joutsa et al. [66]	2012	575	575 PD patients	PD	DA–L-dopa MAO-B inhibitor	Cross-sectional Postal survey	To determine the frequency of ICDs	Prevalence = 34.8% ICDs: sexuality (22.8%) > eating (11.8%) > shopping (10.1%) > gambling (8.8%)
Lipford and Silbert [165]	2012	50	50 RLS patients	RLS	Pramipexole	Retrospective (cohort)	To determine the frequency of ICDs	Prevalence = 10% ($n = 5$) ICDs: eating, sexuality, gambling, shopping
Perez-Lloret et al. [103]	2012	255	203 PD patients (PD + ICD: 52 patients; PD–ICD: 151 patients) 52 post-stroke patients	PD *PD + ICD vs. PD–ICD:* Mean duration: 9.4 (±0.7) vs. 8.8 (±0.5) years	DAA, L-dopa, MAO-B inhibitors, entacapone, amantadine *PD + ICD vs. PD–ICD:* LEDD ≥1050 mg: 63% vs. 42%	Cross-sectional Case-control	To determine the frequency of ICDs	Prevalence among PD patients = 25% (0% among controls) PD + ICD ($n = 52$): Eating (14%) > sexuality (10%) > shopping (6%) > gambling (3%)
Valença et al. [90]	2013	364	152 PD patients (PD + ICD: 28 patients; PD–ICD: 124 patients) 212 healthy controls	PD *PD + ICD vs. PD–ICD:* Mean duration: 7.4 (±4.2) vs. 7.2 (±5.5) years	Pramipexole, amantadine, selegiline, L-dopa *PD + ICD vs. PD–ICD:* Daily pramipexole dosage = 2.9 (±1.2) vs. 0.85 (±1.4) mg LEDD = 732 (±404) vs. 644 (±397) mg	Cross-sectional Case-control	To determine the frequency of ICDs	Prevalence = 18.4% (vs. 4.2% in HC)
Rana et al. [78]	2013	140	140 PD patients	PD	Amantadine, pramipexole, L-dopa	Retrospective chart review	To determine the frequency of ICDs	Prevalence = 5.7% ($n = 8$)

Table 1 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Kim et al. [119]	2013	297	297 PD patients	PD	Stable DRT for at least 3 months	Cross-sectional	To determine the frequency of ICRBs (ICDs, RB, and DDS)	Prevalence of ICRBs = 15.5% Prevalence of ICDs = 11.8% ICDs: sexuality (7.1%) > gambling = eating = shopping (1.3%)
Kim et al. [135]	2013	89	89 PD patients with bilateral STN DBS surgery	PD	Bilateral STN DBS surgery	Longitudinal T1: baseline T2: follow-up (12 months after surgery)	To determine the frequency of ICRBs and severity of ICRB before and after bilateral STN DBS	Prevalence = 22.5% (pre-surgery)/ 25.8% (post-surgery) Preoperative ICRBs (n = 20): resolved (n = 6); improved (n = 7); idem (n = 4); worsened (n = 3) Postoperative de novo ICRBs (n = 9)
Bastiaens et al. [68]	2013	46	PD patients without previous history of ICDs, who were taking a DAA	PD *PD + ICD vs. PD–ICD (baseline):* Mean age at onset (years): 57 (±10) vs. 57 (±9) Mean duration (years): 4 (1–19) vs. 5 (0–14) Motor complications: 61% vs. 25%	DAAs *PD + ICD vs. PD–ICD (follow up:* Peak DAA-LEDD [mg (median)] = 300 (75–450) vs. 165 (50–400)	Longitudinal (4-year prospective cohort study)	To determine the frequency of ICDs	Prevalence = 39.1% 18 cases of ICDs (eating > sexuality > shopping > gambling)
Bayard et al. [72]	2013	149	89 RLS patients: 39 RLS drug-free 50 RLS with DAAs 30 healthy controls	RLS	RLS + DAA: pramipexole or ropinirole	Cross-sectional Case-control Decision-making tasks PSG record for the RLS drug-free group	To determine the frequency of ICDs	Prevalence = drug-free RLS (current: 2.5%/lifetime: 10.2%) and RLS under DAA (current: 2%/lifetime: 6%) Only binge eating

Table 1 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Poletti et al. [97]	2013	805	805 PD patients 593 cognitively preserved 212 demented	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 57 (±12) vs. 66 (±11) Mean duration (years): 10 (±6) vs. 10 (±7)	L-Dopa, DAAs, amantadine, rasagiline	Cross-sectional	To determine the frequency of ICDs	Prevalence = 39.1% Prevalence in cognitively preserved PD patients = 9.6% Prevalence in demented PD patients = 3.8%
Bancos et al. [74]	2014	147	Group A ($n = 77$): prolactinomas and current/past DAA use Group B ($n = 70$): non-functioning pituitary adenoma and no history of DAA use	Prolactinoma	Cabergoline, bromocriptine	Cross-sectional Postal survey	To determine the frequency of ICDs	Prevalence = 24.7% (group A)/ 17.1% (group B)
Callesen et al. [80]	2014	490	490 PD patients	PD	LEDD: Total: 555.4 (392.2) mg DAA: 114.8 (141.9) mg	Cross-sectional	To determine the frequency of ICDs	Prevalence = 35.9% (lifetime)/ 14.9% (current)
Rodríguez-Violante et al. [93]	2014	450	300 PD patients (PD + ICD: 77 patients; PD–ICD: 223 patients) 150 healthy controls (including 25 patients)	PD	L-Dopa, DAAs (especially pramipexole), amantadine *PD + ICD vs. PD–ICD:* DA-LEDD (mg) = 147 (±123) vs. 97 (±125) LEDD (mg) = 638 (±449) vs. 561 (±417)	Cross-sectional Case-control	To determine the frequency of ICDs	Prevalence = 10.6% (5.3% in HC) All HC had only one type of ICD, whereas 4.6% of the PD presented with >1 ICD
Garcia-Ruiz et al. [92]	2014	233	233 PD patients	PD Mean duration: 5.9 years ± 4.1	Oral ($n = 197$): Pramipexole Ropinirole Transdermal ($n = 36$): Rotigotine	Cross-sectional	To determine the frequency of ICDs	Prevalence = 39.1%

Table 1 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Pontieri et al. [82]	2015	155	155 PD patients: 21 PD with PG 36 PD with ICD-NOS 98 No-ICD	PD *PD + PG vs. PD + ICD-NOS vs. PD–ICD:* Mean age at onset (years): 51 (±8) vs. 57 (±10) vs. 61 (±9) Mean duration (years): 8 (±5) vs. 7 (±4) vs. 5 (±3)	*PD + PG vs. PD + ICD-NOS vs. PD–ICD:* DAA-LEDD (mg) = 307 (±275) vs. 316 (±374) vs. 166 (±197) LEDD (mg) = 487 (±625) vs. 388 (±278) vs. 251 (±279) Total LEDD (mg) = 794 (±603) vs. 704 (±509) vs. 416 (±303)	Study cohort	To determine the frequency of ICDs	Prevalence = 36.8% (13.5% for PG)
Todorova et al. [108]	2015	60	60 PD patients: 41 receiving Apo infusion 19 receiving intrajejunal L-dopa infusion	PD *PD + Apo vs. PD + L-dopa:* Mean duration (years): 14 (±5) vs. 16 (±6)	Apo, L-dopa *PD + Apo vs. PD + L-dopa:* Mean dose (mg) = 106 (±24) vs. 1990 (±807) Mean duration of infusion = 16 vs. 16 h/day	Longitudinal (3-year prospective cohort study)	To determine the frequency of ICDs	Apo group (n = 41): 4 patients had pre-existing *ICDs* (1 resolved and 3 attenuated after infusion initiation), 7 patients developed a new ICD (3 resolved, 1 had to stop Apo) L-dopa group (n = 19): 8 patients had pre-existing ICDs (6 resolved and 2 persisted after L-dopa infusion initiation), no new ICDs were observed
Sáez-Francàs et al. [94]	2016	115	115 PD patients: 27 PD + ICD 88 PD–ICD	PD *PD + ICD vs. PD-ICD:* Mean age at onset (years): 53.7 (±10) vs. 60.3 (±9) Mean duration (months): 74.8 (±49) vs. 46.3 (±42)	DAA, L-dopa, MAO-B inhibitors, amantadine *PD + ICD vs. PD-ICD:* DA-EDD (mg) = 216 (±135) vs, 114 (±135) LEDD (mg) = 660 (±403) vs. 440 (±521)	Cross-sectional	To determine the frequency of ICDs	Prevalence = 23.48% Men: sexuality and gambling Women: eating and shopping.

Table 1 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Vela et al. [95]	2016	174	87 EOPD patients 87 age- and gender-matched healthy controls	PD Median disease duration: 5 years	Rasagiline ($n = 48$), L-dopa ($n = 55$) DAAs ($n = 70$): rotigotine, pramipexole, ropinirole, cabergoline	Cross-sectional Case-control	To determine the frequency of ICDs	Prevalence = 58.3% (vs. 32.9% in HC)
Gescheidt et al. [121]	2016	87	49 EOPD 38 age-matched healthy controls	PD Mean duration (years): 11 (3–27)	L-Dopa, DAAs, amantadine, anticholinergics DAA-LEDD (mg) = 300 (105–480) LEDD (mg) = 798 (300–1750) Total LEDD (mg) = 894 256–2050)	Cross-sectional Case-control	To determine the frequency of ICD symptoms	Prevalence of ICD symptoms = 26.5% (10.5% in HC) Prevalence of PG = 8.2% (vs. 0 in HC) Prevalence of HS = 10.2% (vs. 0 in HC)
Patel et al. [166]	2017	312	312 PD patients who were taking DAAS: 156 PD who developed at least 1 AE 156 who did not developed any AE	PD Mean duration (years): 8.5 (±6.2)	Ropinirole, pramipexole, rotigotine DAA-LEDD (mg) = 194 (±117) Total LEDD (mg) = 770 (±430)	Retrospective chart review	To determine the prevalence of DAWS	Prevalence of ICDs = 10.3% DAWS was experienced in 28% of patients who had an ICD ($n = 32$)
Smith et al. [129]	2016	320	PD untreated patients and having a DAT imaging deficit at baseline	PD *Baseline characteristics*: Mean disease duration (months): 6.6	*Follow-up characteristics*: L-dopa, DAAs, MAO-B inhibitors, amantadine	Longitudinal (3-year prospective cohort study)	To determine the incidence of ICD symptoms	Cumulative incidence = 8% (year 1), 18% (year 2), and 25% (year 3) Cumulative incidence rate increased annually in those on DRT and decrease in those not on DRT
Antonini et al. [107]	2016	786	PD patients treated by rotigotine transdermal patch	PD Mean duration (years): 5 (±6)	Rotigotine Duration of exposure (months): 49 (±18)	Post hoc analysis of 6 open-label extension studies	To determine the incidence of ICDs	Prevalence = 9% (63/71 having concomitant L-dopa treatment) Incidence was relatively low during the first 30 months and higher over the next 30 months

Table 1 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Kraemmer et al. [127]	2016	276	PD untreated patients, free of ICD at baseline	PD *Baseline characteristics*: Mean disease duration (months): 6.3 (±6.3)	86% of the patients started DRT during the follow-up 40% of the patients initiated a DAA	Longitudinal (3-year prospective cohort study) Genetic study	To determine the prevalence of ICD behavior during follow-up	Prevalence = 19%
Ramirez Gómez et al. [96]	2017	255	255 PD patients: 70 with ICD 185 No-ICD	PD *PD + ICD vs. PD–ICD*: Median duration (years): 4 vs. 10	DAAs (pramipexole, ropinirole, bromocriptine, piribedil, rotigotine)	Cross-sectional	To determine the prevalence of ICDs	Prevalence = 27.4%

AE adverse event, *Apo* apomorphine, *BED* binge eating disorder, *CS* compulsive shopping, *DA* dopamine, *DAA* dopamine agonist, *DAA-LEDD* dopamine agonist L-dopa equivalent daily dose, *DAT* dopamine transporter, *DAWS* dopamine agonist withdrawal syndrome, *DBS* deep-brain stimulation, *DDS* dopamine dysregulation syndrome, *DRT* dopamine replacement therapy, *EDD* equivalent daily dose, *EOPD* early-onset Parkinson's disease, *HC* healthy control, *HS* hypersexuality, *ICB* impulsive and compulsive behavior, *ICD* impulse control disorder, *ICD-NOS* impulse control disorder not otherwise specified, *ICRB* impulsive control and repetitive behavior disorders, *L-dopa* levodopa, *LEDD* levodopa equivalent daily dose, *MAO-B* monoamine oxidase B, *No-ICD* without impulse control disorder, *PD* Parkinson's disease, *PG* pathological gambling, *PSG* polysomnography, *RB* repetitive behavior disorder, *RLS* restless legs syndrome, *SD* standard deviation, *STN* subthalamic nucleus, + indicates with, − indicates without

Table 2 Drug-related factors

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Pontone et al. [85]	2006	100	PD patients (PD + ICD: 9 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 44.3 (±9) vs. 48.6 (±9) years Mean duration: 4.6 (±62.2) vs. 6.2 (±5.5) years	Pramipexole, ropinirole, amantadine, entacapone, selegiline, L-dopa *PD + ICD vs. PD–ICD:* L-dopa dose = 627 (±281) vs. 520 (±450) mg	Cross-sectional	To determine the correlates of ICDs	DAAs (as a class, concerning only pramipexole or ropinirole) use Significant association with pramipexole (and not with ropinirole)
Weintraub et al. [86]	2006	272	PD patients	PD	Pramipexole, ropinirole, pergolide, L-dopa, amantadine	Cross-sectional	To determine the correlates of ICDs	DAA use No significant association with a specific DAA (ropinirole, pramipexole, or pergolide) Significant association with higher doses of DAAs
Grosset et al. [98]	2006	388	PD patients	PD	Pramipexole, ropinirole, pergolide, L-dopa, amantadine, entacapone, selegiline, anticholinergic	Cross-sectional	To determine the correlates of excessive gambling	Higher daily doses of pramipexole
Giladi et al. [105]	2007	383	193 PD patients (PD + ICD: 27 patients; PD–ICD: 166 patients) 190 age- and gender-matched HCs	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 51.5 (±12.2) vs. 58.7 (±12.1) Mean duration (years): 10.3 (±4.9) vs. 9.7 (±6.6)	Ropinirole, pergolide, cabergoline, apomorphine, amandatine, selegiline, entacapone	Cross-sectional	To determine the correlates of ICDs	Longer duration of treatment with DAAs
Crockford et al. [87]	2008	140	Not demented patients, with moderate to severe PD	PD	Pramipexole, ropinirole, pergolide, bromocriptine, L-dopa LEDD (mg) = 707 (±402)	Cross-sectional	To determine the correlates of problem gambling and PG	DAA use

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Abler et al. [109]	2009	12	Female RLS patients	RLS Mean duration (years): 4 (±2)	Pramipexole, ropinirole, cabergoline DAA doses (mg pramipexole equivalent) = 0.5 (±0.2)	Crossover ('on' and 'off' DAA medication) fMRI coupled with a gambling game task	To investigate the underlying neurobiology	Change in the neural signaling of reward expectation (mesolimbic dopaminergic hyperactivation) with DAA medication, underlying a sensitization towards ICDs
Fan et al. [88]	2009	444	312 PD patients (PD + ICD: 11 patients; PD–ICD: 301 patients) 132 controls (spouses/caregivers of the patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 59 (±7) vs. 60 (±11) Mean duration (years): 5 (±3) vs. 6 (±3)	L-dopa, piribedil, pramipexole, amantadine, pergolide, ergocriptine, bromocriptine *PD + ICD vs. PD–ICD:* Total LEDD = 487 (±289) vs. 392 (±224) mg	Cross-sectional	To determine the correlates of ICDs	DAA use
van Eimeren et al. [110]	2009	8	PD patients	Patients with early-stage PD Mean duration (years): 4 (±3)	*Combination of* L-dopa dose (mg/day) = 594 (±290) *And* Pramipexole dose (mg/day) = 2.3 (±1.1)	Crossover (off medication, after L-dopa and after an equivalent dose of pramipexole fMRI coupled with a probabilistic reward task	To investigate the underlying neurobiology	With pramipexole: tonic dopaminergic stimulation specifically diminished reward processing in the lateral OFC DAAs may abate negative reinforcement in feedback-based learning This finding is drug-specific (not observed after L-dopa)
van Eimeren et al. [111]	2010	14	14 PD patients: 7 with DAA-induced PG 7 without PG (matched for DRT, age and PD duration and severity)	PD The 2 groups of patients were matched for PD duration and severity	The 2 groups of patients were matched for DRT	Cross-sectional Case-control PET scanning coupled with a card selection game	To investigate the underlying neurobiology	In PD + DAA-induced PG: significant DAA-induced reduction of neuronal activity in brain areas that are implicated in impulse control and response inhibition (lateral OFC, RCZ, amygdala, GPe).

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Kenangil et al. [101]	2010	554	PD patients (PD + ICD: 33 patients; PD–ICD: 65 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 49 (±9) vs. 52 (±11) Mean duration (years): 8 (±5) vs. 7 (±5)	Pergolide, cabergoline, pramipexole, ropinirole, piribedil, lisuride *PD + ICD vs. PD–ICD:* DAA-LEDD (mg) = 369 (±181) vs. 319 (±208) Total LEDD (mg) = 702 (±2369) vs. 640 (±357)	Cross-sectional	To determine the correlates of ICDs	No association between ICDs and doses of DAAs
Weintraub et al. [84]	2010	3090	*DOMINION study*	PD	DAAs and/or L-dopa (n = 3031) DAAs (mean daily dosage and LEDDs): Pramipexole: 3.1 (SD = 1.7) and 306.9 (SD = 168.2) mg Ropinirole: 11.1 (SD = 6.6) and 277.9 (SD = 164.9) mg Pergolide: 2.9 (SD = 1.7) and 286.6 (SD = 169.3) mg	Cross-sectional Case-control (matching on age, sex and DAA treatment)	To determine the correlates of ICDs	Both DAAs and L-dopa use, with the OR nearly twice as high for DAAs
Lee et al. [102]	2010	1167	PG patients	PD Mean age at onset (years): 58 (±11) Mean duration (years): 7 (±4)	Stable DRT for at least 3 months Mean duration of DRT: 5.0 years (± 3.8)	Cross-sectional	To determine the correlates of ICRBs	*Multivariate analysis*: DAAs: dose-response relationship with the compulsive shopping, gambling, and sexual behaviors L-dopa: dose–response relationship with punding
Voon et al. [112]	2010	44	14 PD + ICD patients 14 PD patients 16 medication-free normal controls	PD	DAAs ± L-dopa DAA-LEDD (mg) = 161.5 (SD = 43.5) for PD ± ICD and 155.5 (SD = 57.3) for PD	Crossover with a within- and between-subjects design ('on' and 'off' DAA medication)	To investigate the underlying neurobiology	Group × medication interaction effect: *DAA status* was associated with increased impulsive choice and shorter reaction time and decision conflict reaction time in PD + ICD but not in PD Higher rate of spatial working memory errors in PD + ICD Higher rate of visual hallucinations or illusions in PD

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Pallanti et al. [163]	2010	24	24 PD patients who underwent STN DBS	PD	STN DBS	Cross-sectional Patient-and-relative-completed survey	To investigate the underlying neurobiology	Non-punders: started bilateral STN DBS on average 1.96 years before the punders
Sohtaoglu et al. [104]	2010	22	22 PD patients with ICDs	PD Mean age at onset (years): 47 (±9) Mean duration (years): 11 (±6)	DAA (mg/day) = 3.7 (±1.7) L-dopa (mg/day) = 239 (±252)	Longitudinal T1: ICDs diagnosis T2: follow-up	To evaluate the outcome of ICDs	Recovery from compulsive behaviors after reducing dosage of DAAs for 16/22 patients
Voon et al. [114]	2011	44	14 PD + ICD 14 PD 16 medication-free normal controls	PD	DDAs	Crossover with a within- and between-subjects design ('on' and 'off' DAA medication) fMRI coupled with a gamble risk-taking task	To investigate the underlying neurobiology	PD + ICD made more risky choices at lower 'gamble risk' than PD DAAs in PD + ICS enhanced sensitivity to gamble risk with the opposite effect in PD. PD + ICS have an increased risk-taking bias compared to PD when there is only the prospect of gain, but not where there are both prospects of gain and loss DAAs may enhance an unconscious bias towards risk in susceptible individuals, underpinned by decreased coupling of neural evaluation and risk in the ventral striatum, orbitofrontal cortex and anterior cingulate
Voon et al. [70]	2011	140	RLS ± ICD	RLS	DAAs (ropinirole 2–4.5 mg/day: $n = 3$; pramipexole 0.72–1.4 mg/day: $n = 3$; lisuride 2.5 mg/day: $n = 1$; cabergoline 3 mg/day: $n = 1$) L-dopa (100 mg/day: $n = 3$)	Cross-sectional	To determine the correlates of ICDs	Higher DAAs dose (mean DAA dose as LEDD mg/day: 63.7 [SD = 52.7] vs. 26.7 [SD = 26.4])

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Hassan et al. [106]	2011	321	DAA-treated PD patients	PD	Ropinirole and pramipexole, L-dopa, selegiline, rasagiline, amantadine, entacapone	Cohort (retrospective)	To determine the correlates of ICDs	*Univariate analysis*: Median duration of DAA use Therapeutic dose Target dose Concurrent L-dopa Surgery
Auyeung et al. [136]	2011	213	PD patients (PD + ICD: 198 patients; PD–ICD: 15 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 46 (±6) vs. 59 (±11) Mean duration (years): 14 (±6) vs. 9 (±5)	Bromocriptine, ropinirole, pramipexole, rotigotine, L-dopa *PD + ICD vs. PD–ICD:* DAA-LEDD (mg) = 277 (±147) vs. 85 (±98) Total LEDD (mg) = 1215 (±635) vs.634 (±330)	Cross-sectional	To determine the correlates of ICDs	Higher dose of DAA exposure
Ávila et al. [167]	2011	25	PD patients who developed ICBs	PD Mean duration (years): 4 (1–21)	Pramipexole, ropinirole, pergolide, cabergoline, rotigotine T1: 18/25 were taking DAA DAA-LEDD (mg) = 286 (±118)	Longitudinal T1: ICBs diagnosis T2: follow-up	To analyze the long-term outcomes in relation to changes in DRT and psychiatric therapy	Significant association between DRT and ICD, but not with punding Full or partial remission of the ICDs symptoms in 5 patients who did not reduce DRT
Zahodne et al. [164]	2011	96	96 PD patients (PD + BED: 9 patients; PD–BED: 87 patients)	PD *PD + BED vs. PD–BED:* Mean age at onset (years): 58 (±8) vs. 56 (±13) Mean duration (months): 124 (±57) vs. 120 (±109)	DAA STN DBS surgery	Cross-sectional	To determine the correlates of BED and subthreshold BED	History of DBS No significant association with DAAs

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Claassen et al. [115]	2011	41	41 DAA-treated PD patients: 22 with ICDs 19 No-ICDs	PD	Pramipexole, ropinirole, L-dopa	Cross-sectional Crossover with a within- and between-subjects design ('on' and 'off' DAA medication) Risk task	To investigate the underlying neurobiology	DAAs increased risk-taking in PD patients with ICDs, but not for those without ICDs (no difference in 'off' state)—this effect is maintained with low doses of DA agonists Risk adjustment after negative outcomes was not influenced by DAA state, ICD status, or their interaction Importance of DAA doses in explaining risk behavior
Lim et al. [137]	2011	200	PD patients	PD	Piribedil, pramipexole, ropinirole, bromocriptine, amantadine Low dosages of DRT	Cross-sectional	To determine the correlates of ICDs	*Multivariate analysis*: No significant association
Solla et al. [75]	2011	349	349 PD patients: 87 without MC 262 with MC	PD *PD + MC vs. PD–MC:* Mean age at onset (years): 62 (±10) vs. 63 (±10) Mean duration (years): 11 (±6) vs. 6 (±6)	L-Dopa, DAAs *PD + MC vs. PD-MC:* DAA-LEDD (mg) = 73 (±106) vs. 64 (±79) Total LEDD (mg) = 606 (±324) vs. 411 (±238)	Cross-sectional	To determine the correlates of motor complications	All the patients with ICDs were taking significantly higher LEDD, with concomitant more frequent use of DAAs (with the exception of patients with compulsive shopping)
Vallelunga et al. [168]	2011	89	89 PD patients: 48 No-ICD 41 with ICDs	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 53 (±10) vs. 57 (±11) Mean duration (years): 9 (±4) vs. 11 (±8)	*PD + ICD vs. PD–ICD:* DAA use: 40/41 vs. 38/48 DAA-LEDD (mg) = 168 (±114) vs. 124 (±114)	Cross-sectional Case-control study	To determine the correlates of ICDs	*Univariate analysis*: No significant association with variants of DRD2 *Taq1A*, COMT and DAT1

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Shotbolt et al. [117]	2012	50	50 PD patients with a pre-operative assessment	PD	DBS	Longitudinal	To discuss ICD/DDS and DBS pre-operative and post-operative relationships	29 patients proceeded to surgery (including 4/8 patients who had ICDs and/or DDS) 1 has shown recurrence after 18 months of being free from ICD. In the remaining 3, none has shown recurrence at follow-up ranging from 17 to 41 months
Politis et al. [89]	2012	24	24 PD patients: 12 with hypersexuality 12 controls	PD		Cross-sectional Case-control study with a within- and between-subjects design ('on' and 'off' DA medication) fMRI coupled with exposure to sexual cues	To investigate the underlying neurobiology	*Univariate analysis*: PD + hypersexuality Significantly more DAAs and significantly less L-DOPA Decreases in activation during the presentation of sexual cues relative to rest when the patients were OFF medication, but not ON medication DA drugs may release inhibition within local neuronal circuits in the cerebral cortex that may contribute to compulsive sexual behavior
Leroi et al. [76]	2012	99	99 PD patients: 35 PD + ICD 26 PD + apathy 38 control PD	PD	57.6% were taking DRT	Cross-sectional Case-control	To determine the correlates of ICDs and apathy	*Univariate analysis*: PD + ICD vs. PD + apathy Higher LEDD
Perez-Lloret et al. [103]	2012	255	203 PD patients (PD + ICD: 52 patients; PD–ICD: 151 patients) 52 post-stroke patients	PD *PD + ICD vs. PD–ICD:* Mean duration: 9.4 years (±0.7) vs. 8.8 (±0.5)	DAA, L-dopa, MAO-B inhibitors, entacapone, amantadine *PD + ICD vs. PD–ICD:* LEDD ≥1050 mg: 63% vs. 42%	Cross-sectional Case-control	To determine the correlates of ICDs	Exposure to DAAs or MAO-B inhibitors, with a dose-response fashion (non-linear dose–response relationship between DAAs and frequency of ICD symptoms)
Joutsa et al. [100]	2012	270	270 PD patients: 135 no ICDs 22 novel ICDs 31 resolved ICDs 82 stable ICDs	PD	DAAs, L-dopa MAO-B inhibitor	Longitudinal T1: baseline T2: follow-up (15 months later)	To determine the correlates of ICDs development and resolution	*Resolution of ICDs*: Lower DAA dose at baseline *Development of a novel ICDs*: No significant association with DAAs doses

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Limotai et al. [77]	2012	1040	PD patients, excluding those who were never exposed to DAA (PD + ICD: 89 patients; PD–ICD: 951 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 52 (±10) vs. 59.7 (±12) Mean duration (years): 11.5 (±6.1) vs. 11.3 (±6.8)	*PD + ICD vs. PD–ICD:* LEDD = 971 (±663) vs. 672 (±512) mg DAA-LEDD = 292 (±184) vs. 142 (±176) mg Total LEDD = 1122 (±644) vs. 779 (±543) mg	Retrospective (cohort)	To determine the correlates of DAWS, DDS, and ICDs	*Univariate analysis concerning ICDs*: Higher doses of DAA, L-dopa, and total dopaminergic medications More frequent DAWS and DDS
Rana et al. [78]	2013	140	140 PD patients	PD	Amantadine, pramipexole, L-dopa	Retrospective chart review	To determine the correlates of ICDs	5 common variables among the patients who developed ICDs, including: maximum dose of the drug; DAA use
Valença et al. [90]	2013	364	152 PD patients (PD + ICD: 28 patients; PD–ICD: 124 patients) 212 HCs	PD *PD + ICD vs. PD–ICD:* Mean duration: 7.4 (±4.2) vs. 7.2 (±5.5) years	Pramipexole, amantadine, selegiline, L-dopa *PD + ICD vs. PD–ICD:* Daily pramipexole dosage = 2.9 (±1.2) vs. 0.85 (±1.4) mg LEDD = 732 (±404) vs. 644 (±397) mg	Cross-sectional Case-control	To determine the correlates of ICDs	Higher dose of pramipexole
Leroi et al. [79]	2013	110	90 PD patients: 35 PD with ICD 55 PD without ICD 20 HCs	PD	Stable DRT for at least 2 months	Cross-sectional Case-control study with a within- and between-subjects design ('on' and 'off' DA medication) Stop and delay-discounting tasks Genotyping for a subset of PD patients	To investigate the underlying neurobiology	*Univariate analysis ICD vs. Non-ICD*: ICD were associated with more complications of therapy and higher LEDD PD + ICD/'on' medication: no impairment on cognitive flexibility; greater impulsive choice; no difference on the response inhibition PD + ICD/'off' medication: no difference in impulsive choice

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Kim et al. [135]	2013	89	89 PD patients with bilateral STN DBS surgery	PD	Bilateral STN DBS surgery	Longitudinal T1: baseline T2: follow-up (12 months after surgery)	To determine the effect of STN DBS on ICRB	20/89 patients had ICRB in the preoperative period, which improved for 13 of them 9 patients developed de novo ICRB after surgery No significant association between postoperative worsening or de novo ICRBs and LEDD levels
Bastiaens et al. [68]	2013	46	PD without previous history of ICDs, who were taking a DAA	PD *PD + ICD vs. PD–ICD (baseline):* Mean age at onset (years): 57 (±10) vs. 57 (±9) Mean duration (years): 4 (1–19) vs. 5 (0–14) Motor complications: 61% vs. 25%	DAAs *PD + ICD vs. PD–ICD (follow up):* Peak DAA-LEDD (mg, median) = 300 (75–450) vs. 165 (50–400)	Longitudinal (4-year prospective cohort study)	To determine the correlates of ICDs	Higher peak DAA dose Non-significant results: DAA treatment duration, cumulative DAA exposure, type of molecule, concomitant L-dopa, L-dopa dosage, total LEDD, DRT duration
Bayard et al. [72]	2013	149	89 RLS patients: 39 RLS drug-free 50 RLS with DAA 30 HCs	RLS	RLS + DAA: pramipexole or ropinirole	Cross-sectional Case-control Decision-making tasks PSG record for the RLS drug-free group	To investigate the underlying neurobiology	(1) ICDs, impulsivity, and addictive behaviors are relatively uncommon in patients with RLS, with no difference between drug-free and DAA-treated patients (2) Reduced decision-making performances in patients with RLS when the outcome probabilities are unknown, with no difference between drug-free and DAA-treated patients

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Sharp et al. [169]	2013	36	18 PD patients 18 age-matched HCs	PD	L-Dopa (LEDD : 631.15 mg/day) 1 h before the second decision-making task	Cross-sectional Case-control Vancouver gambling task	To investigate the underlying neurobiology	No significant difference between PD patients (ON or OFF medication) and HC when evaluating gains OFF L-dopa: PD patients show risk-aversion for large losses ON L-dopa: PD patients have normal perception of magnitude and probability for both loss and gain
Poletti et al. [97]	2013	805	805 PD patients 593 cognitively preserved 212 demented	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 57 (±12) vs. 66 (±11) Mean duration (years): 10 (±6) vs. 10 (±7)	L-Dopa, DAAs, amantadine, rasagiline	Cross-sectional	To determine the correlates of ICDs	DAA use (no difference between pramipexole and ropinirole) L-dopa use
Callesen et al. [80]	2014	490	490 PD patients	PD	Total-LEDD: 555.4 (392.2) mg DAA-LEDD: 114.8 (141.9) mg	Cross-sectional	To determine the correlates of ICDs	Higher total LEDD (no difference on DAA-LEDD)
Moore et al. [91]	2014	2.7 million ADE reports	FDA ADE reporting system		6 FDA-approved DAAs: pramipexole, ropinirole, cabergoline, bromocriptine, rotigotine, apomorphine	Retrospective disproportionality analysis during the 10-year period	To analyze serious ADR reports about ICDs	1580 reports of ICDs (+ gambling): 710 for DAAs and 870 for other drugs The 6 DAAs had a strong signal, the strongest with pramipexole and ropinirole (preferential affinity for the dopamine D_3 receptor).

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Sachdeva et al. [81]	2014	73	73 PD patients: 20 with CSB 11 with ICD–CSB 42 PD controls	PD *PD + CSB vs. PD + ICD vs. PD–ICD:* Mean duration (months): 96 (±48) vs. 72 (±72) vs. 72 (±66)	*PD + CSB vs. PD + ICD vs. PD–ICD:* LEDD = 941 (±668) vs. 800 (±619) vs. 706 (±693) mg	Cross-sectional Case-control	To determine the correlates of CSB	*PD ± CSB vs. PD controls*: Higher LEDD
Garcia-Ruiz et al. [92]	2014	233	233 PD patients	PD Mean duration: 5.9 years ± 4.1	*Oral (n = 197)*: Pramipexole Ropinirole *Transdermal (n = 36)*: Rotigotine	Cross-sectional	To determine the correlates of ICDs	Oral DAAs Rasagiline use
Djamshidian et al. [113]	2014	61	44 PD patients: 17 PD + L-Dopa + DAA 12 PD + L-Dopa only 15 PD + ICDs 17 HCs	PD	DAAs: pramipexole ($n = 15$), ropinirole ($n = 9$), rotigotine ($n = 1$) and apomorphine ($n = 1$) L-dopa ($n = 12$)	Cross-sectional Case-control Perceptual inference and reaction time tasks	To investigate the underlying neurobiology	*PD ± ICD vs. HC*: Faster reaction times, presumably reflecting lower decision thresholds and poorer information sampling *PD with L-dopa ± DAA vs. with L-Dopa only*: Faster reaction times
Rodríguez-Violante et al. [93]	2014	450	300 PD patients (PD + ICD: 77 patients; PD–ICD: 223 patients) 150 HCs (including 25 patients)	PD	L-Dopa, DAAs (especially pramipexole), amantadine *PD + ICD vs. PD–ICD:* DAA-LEDD (mg) = 147 (±123) vs. 97 (±125) LEDD (mg) = 638 (±449) vs. 561 (±417)	Cross-sectional Case-control	To determine the correlates of ICDs	DAA use Higher DAA-LEDD

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Olley et al. [120]	2015	40	40 PD patients: 20 PG_PD 20 NG_PD	PD *PG_PD vs. NG_PD:* Mean age at onset (years): 56.4 (±9) vs. 59.4 (±8) Mean duration (years): 8 (±5) vs. 7.9 (±4)	Cabergoline, pramipexole, pergolide, bromocriptine, L-dopa	Cross-sectional Case-control	To explore the temporal relationships between problem gambling and DRT	90% of PG_PD identified a noticeable increase in their gambling behaviors and urges after commencing DRT, within 3 or 6 months 80% of PG_PD changed the dosage, class, or type of DRT, and within this group, 30% had ceased gambling and 50% had decreased gambling behaviors
Claassen et al. [116]	2015	36	24 PD patients: 12 PD + ICDs 12 PD–ICD 12 HCs	PD	All patients were taking DAAs and about half were taking concomitant L-dopa	Cross-sectional Case-control study with a within- and between-subjects design ('on' and 'off' DAA) Stop-signal task	To investigate the underlying neurobiology	No significant difference on motor-impulsivity between PD-ICD and HC PD + ICDs stopped faster than both other groups, in both medication states ('on' and 'off' DAAs) There was an opposite effect on Go Reaction Time between patients with DAA monotherapy (DAA administration speeds Go Reaction Time) and those with L-dopa co-therapy (DAA administration slows Go Reaction Time)
Pontieri et al. [82]	2015	155	155 PD patients: 21 PD + PG 36 PD + ICD-NOS 98 No-ICD	PD *PD + PG vs. PD + ICD-NOS vs. PD–ICD:* Mean age at onset (years): 51 (±8) vs. 57 (±10) vs. 61 (±9) Mean duration (years): 8 (±5) vs. 7 (±4) vs. 5 (±3)	*PD + PG vs. PD + ICD-NOS vs. PD–ICD:* DAA-LEDD (mg) = 307 (±275) vs. 316 (±374) vs. 166 (±197) LEDD (mg) = 487 (±625) vs. 388 (±278) vs. 251 (±279) Total LEDD (mg) = 794 (±603) vs. 704 (±509) vs. 416 (±303)	Study cohort	To determine the correlates of ICDs	PD patients with PG and ICD-NOS vs. No-ICD: higher doses of DRT

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Sáez-Francàs et al. [94]	2016	115	115 PD patients: 27 PD + ICD 88 PD–ICD	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 53.7 (±10) vs. 60.3 (±9) Mean duration (months): 74.8 (±49) vs. 46.3 (±42)	DAA, L-dopa, MAO-B inhibitors, amantadine *PD + ICD vs. PD–ICD:* DAA-LEDD (mg) = 216 (±135) vs. 114 (±135) LEDD (mg) = 660 (±403) vs. 440 (±521)	Cross-sectional	To determine the correlates of ICDs	DAA use
Vela et al. [95]	2016		87 EOPD patients 87 age- and gender-matched HCs	PD Median disease duration: 5 years	Rasagiline ($n = 48$), L-dopa ($n = 55$) DAAs ($n = 70$): rotigotine, pramipexole, ropinirole, cabergoline	Cross-sectional Case-control	To determine the correlates of ICDs	DAA use
Chang et al. [170]	2016	15	15 PD patients treated with LCIG	PD	Intraduodenal LCIG infusion during 16 h/day for 6 months Stop DA agonists: oral L-dopa/carbidopa authorized for nocturnal 'off' symptoms	Longitudinal T1: baseline T2: follow-up (6 months) T2: follow-up (12 months) Open-label study	To assess the efficacy and ADE profile of LCIG for the treatment of advanced PD	(1) *Efficacy*: 66% had a reduction in total LEDD, improvement of the part III of the UPDRS (at 6 and 12 months), reduction of the daily 'off' period and increase of the daily 'on' period (at 6 and 12 months) and improvement of functioning and well-being (PDQ-39) (at 6 and 12 months) (2) *ADEs*: The most common ADEs were reversible peripheral neuropathy secondary to vitamin B12 ± B6 deficiency (40%), local tube problems (40%), and ICDs or DDS (27%) 3 patients who had prior ICD with DAAs did not develop ICD or DDS with LCIG infusion LEDD increased in patients with ICD and decreased in patients without ICD

Table 2 continued

Studies	Year	Sample size	Participants	Disease (duration, type, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Krishnamoorthy et al. [83]	2016	455	170 PD patients: 70 with ICDs 100 No-ICD 285 HCs	PD	L-Dopa (81%) DAAs (pramipexole or ropinirole) (58%)	Cross-sectional Case-control	To determine the correlates of ICDs	DDA use Higher LEDD
Gescheidt et al. [121]	2016	87	49 EOPD 38 age-matched HCs	PD Mean duration (years): 11 (3–27)	L-Dopa, DAAs, amantadine, anticholinergics DAA-LEDD (mg) = 300 (105–480) LEDD (mg) = 798 (300–1750) Total LEDD (mg) = 894 (256–2050)	Cross-sectional Case-control	To determine the correlates of ICD symptoms	*Univariate analysis*: Higher frequency of PG in EOPD treated with DAAs
Ramirez Gómez et al. [96]	2017	255	255 PD patients: 70 with ICD 185 No-ICD	PD *PD + ICD vs. PD-ICD:* Median duration (years): 4 vs. 10	DAAs (pramipexole, ropinirole, bromocriptine, piribedil, rotigotine)	Cross-sectional	To determine the correlates of ICDs	DAA use

ADE adverse drug event, *ADR* adverse drug reaction, *BED* binge eating disorder, *CSB* compulsive sexual behavior, *COMT* catechol-*O*-methyltransferase, *DA* dopamine, *DAA* dopamine agonist, *DAA-LEDD* dopamine agonist L-dopa equivalent daily dose, *DAT* dopamine transporter, *DAWS* dopamine agonist withdrawal syndrome, *DBS* deep-brain stimulation, *DDS* dopamine dysregulation syndrome, *DRT* dopamine replacement therapy, *EOPD* early-onset Parkinson's disease, *FDA* Food and Drug Administration, *fMRI* functional magnetic resonance imaging, *GPe* external pallidum, *HC* healthy control, *ICB* impulsive and compulsive behavior, *ICD* impulse control disorder, *ICD-NOS* impulse control disorder not otherwise specified, *ICRB* impulsive control and repetitive behavior disorders, *LCIG* levodopa–carbidopa intestinal gel, L-dopa levodopa, *LEDD* levodopa equivalent daily dose, *MAO-B* monoamine oxidase B, *MC* motor complications, *NG_PD* Parkinson's disease without problem gambling, *No-ICD* without impulse control disorder, *OFC* orbitofrontal cortex, *PD* Parkinson's disease, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *PET* positron emission tomography, *PG_PD* Parkinson's disease with problem gambling, *PG* pathological gambling, *PSG* polysomnography, *RCZ* rostral cingulated zone, *RLS* restless legs syndrome, *SD* standard deviation, *STN* subthalamic nucleus, *Total LEDD* LEDD+DAA-LEDD, *UPDRS* Unified Parkinson's Disease Rating Scale, + indicates with, − indicates without

Table 3 Patient-related factors

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Pontone et al. [85]	2006	100	PD patients (PD + ICD: 9 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 44.3 (±9) vs. 48.6 (±9) years Mean duration: 4.6 (±62.2) vs. 6.2 (±5.5) years	Pramipexole, ropinirole, amantadine, entacapone, selegiline, L-dopa *PD + ICD vs. PD–ICD:* L-dopa dose = 627 (±281) vs. 520 (±450) mg	Cross-sectional	To determine the correlates of ICDs	Discrete symptoms of depressed mood, irritability, appetite changes, and disinhibition
Giladi et al. [105]	2007	383	193 PD patients (PD + ICD: 27 patients; PD–ICD: 166 patients) 190 age- and gender-matched HCs	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 51.5 (±12.2) vs. 58.7 (±12.1) years Mean duration: 10.3 (±4.9) vs. 9.7 (±6.6) years	Ropinirole, pergolide, cabergoline, apomorphine, amandatine, selegiline, entacapone	Cross-sectional	To determine the correlates of ICDs	Male gender
Crockford et al. [87]	2008	140	Not demented patients, with moderate to severe PD	PD	Pramipexole, ropinirole, pergolide, bromocriptine, L-dopa LEDD = 707 (±402) mg	Cross-sectional	To determine the correlates of problem gambling and PG	Younger age No significant association with psychiatric/SUD co-morbidity
Fan et al. [88]	2009	444	312 PD patients (PD + ICD: 11 patients; PD–ICD: 301 patients) 132 controls (spouses/caregivers of the patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 58.7 (±6.7) vs. 60.1 (±10.6) years Mean duration: 5.3 (±2.5) vs. 5.7 (±2.9) years	L-Dopa, piribedil, pramipexole, amantadine, pergolide, ergocriptine, bromocriptine *PD + ICD vs. PD–ICD:* Total LEDD (mg) = 487 (±289) vs. 392 (±224)	Cross-sectional	To determine the correlates of ICDs	Alcohol daily use

Table 3 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Weintraub et al. [84]	2010	3090	*DOMINION study*	PD	DAAs and/or L-dopa ($n = 3031$) DAAs (mean daily dosage and LEDDs): Pramipexole 3.1 (±1.7) and 306.9 (±168.2) mg Ropinirole: 11.1 (±6.6) and 277.9 (± 164.9) mg Pergolide: 2.9 (±1.7) and 286.6 (±169.3) mg	Cross-sectional Case-control (matching on age, sex, and DAA treatment)	To determine the correlates of ICDs	Living in the USA Younger age Being unmarried Current nicotine use Family history of gambling problems
Cilia et al. [128]	2010	43	29 PD patients: 8 PD with PG 21 PD–ICD (matched for demographic, clinical features, and mean daily DRT intake) 14 HCs	PD *PD + PG vs. PD–ICD:* Mean duration: 6 (±2) vs. 6 (±2) years	L-Dopa + DAAs *PD + PG vs. PD–ICD:* Total LEDD (mg) = 831 (±294) vs. 852 (±301) DAA-LEDD (mg) = 241 (±118) vs. 252 (±121)	Cross-sectional Case-control Imaging study (SPECT of DAT)	To investigate the underlying neurobiology	DAT density differed between the 3 groups in both dorsal and ventral striata bilaterally Post hoc analysis: reduced tracer binding in the ventral striatum for PD with PG compared to PD without ICD
Lee et al. [102]	2010	1167	PG patients	PD Mean age at onset: 58.3 (±10.5) years Mean duration: 6.6 (±4.3) years	Stable DRT for at least 3 months Mean duration of DRT: 5.0 years (±3.8)	Cross-sectional	To determine the correlates of ICRBs	Univariate analysis: male gender for gambling and sexuality
Pourcher et al. [123]	2010	97	97 RLS patients: 32 untreated patients without compulsions 53 DAA-treated patients without compulsions 12 DAA-treated patients with compulsions	RLS	Stable DAA (average dose 0.52 mg pramipexole equivalent)	Longitudinal T1: baseline T2: 4 months T3: 8 months	To determine the correlates of motor/behavioral compulsions	More stress, depression, and sleep problems

Table 3 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Voon et al. [122]	2011	564	564 PD patients: 282 with ICDs 282 No-ICD (matching on age, gender, and DAA treatment)	PD	DAAs ± L-dopa	Cross-sectional Case-control *(DOMINION study)*	To determine the correlates of ICDs	Higher depression, anxiety, and obsessive–compulsive symptoms scores Higher novelty-seeking and impulsivity scores Greater choice impulsivity
Voon et al. [70]	2011	140	RLS ± ICD	RLS	DAAs (ropinirole 2–4.5 mg/day: $n = 3$; pramipexole 0.72–1.4 mg/day: $n = 3$; lisuride 2.5 mg/day: $n = 1$; cabergoline 3 mg/day: $n = 1$) L-dopa 100 mg/day: $n = 3$	Cross-sectional	To determine the correlates of ICDs	Female gender History of experimental drug use Family history of gambling disorders
Auyeung et al. [136]	2011	213	PD patients (PD + ICD: 198 patients; PD–ICD: 15 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 45.7 (±5.6) vs. 59 (±10.8) years Mean duration: 13.5 (±5.6) vs. 8.9 (±4.8) years	Bromocriptine, ropinirole, pramipexole, rotigotine, L-dopa *PD + ICD vs. PD–ICD:* DAA-LEDD = 277 (±147) vs. 85 (±98) mg Total LEDD = 1215 (±635) vs. 634 (±330) mg	Cross-sectional	To determine the correlates of ICDs	History of anxiety and depression
Lim et al. [137]	2011	200	200 PD patients	PD	Piribedil, pramipexole, ropinirole, bromocriptine, amantadine Low dosages of DRT	Cross-sectional	To determine the correlates of ICDs	Male gender

Table 3 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Vallelunga et al. [168]	2011	89	89 PD patients: 48 No-ICD 41 with ICDs	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 52.7 (±10.1) vs. 57.3 (±10.7) years Mean duration: 9 (±4.4) vs. 11.4 (±7.8) years	*PD + ICD vs. PD–ICD:* DAA use: 40/41 vs. 38/48 DAA-LEDD = 168 (±114) vs. 124 (±114) mg	Cross-sectional Case-control study	To determine the correlates of ICDs	*Univariate analysis*: Younger age
O'Sullivan et al. [131]	2011	18	18 PD patients: 7 No-ICD 11 with ICDs	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 45.1 (±11.2) vs. 47 (±8.8) years Mean duration: 11.9 (±11.3) vs. 10.7 (±6.4) years	*PD + ICD vs. PD–ICD:* DAA-LEDD = 62 (±92) vs. 241 (±143) mg LEDD = 636 (±325) vs. 708 (±319) mg	Cross-sectional Case-control study 3 ^{11}C-raclopride PET scans	To determine the correlates of ICDs	*PD patients with ICDs vs. without*: No significant differences in baseline dopamine D_2 receptor availability Greater reduction of ventral striatum ^{11}C-raclopride binding potential following reward-related cue exposure, relative to neutral cue exposure, following L-dopa challenge
Limotai et al. [77]	2012	1 040	PD patients, excluding those who were never exposed to DAA (PD + ICD: 89 patients; PD–ICD: 951 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 52 (±10) vs. 59.7 (±12) years Mean duration: 11.5 (±6.1) vs. 11.3 (±6.8) years	*PD + ICD vs. PD–ICD:* LEDD = 971 (±663) vs. 672 (±512) mg DAA-LEDD = 292 (±184) vs. 142 (±176) mg Total LEDD = 1122 (±644) vs. 779 (±543) mg	Retrospective (cohort)	To determine the correlates of DAWS, DDS, and ICDs	*Univariate analysis concerning ICDs*: Male gender Younger age
Leroi et al. [76]	2012	99	99 PD patients: 35 PD + ICD 26 PD + apathy 38 control PD	PD	57.6% were taking DRT	Cross-sectional Case-control	To determine the correlates of ICDs and apathy	*Univariate analysis*: PD + ICD vs. PD + apathy Higher level of anxiety.

Table 3 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Joutsa et al. [100]	2012	270	270 PD patients: 135 no ICD 22 novel ICD 31 resolved ICD 82 stable ICD	PD	DAAs, L-dopa MAO-B inhibitor	Longitudinal T1: baseline T2: follow-up (15 months later)	To determine the correlates of ICDs	*Resolution of ICD*: Female gender *Development of a novel ICD*: Concurrent increase in depression scores
Joutsa et al. [66]	2012	575	575 PD patients	PD	DA–L-dopa MAO-B inhibitor	Cross-sectional Postal survey	To determine the correlates of ICDs	Higher depression score Male gender Age $\leq$65 years
Perez-Lloret et al. [103]	2012	255	203 PD patients (PD + ICD: 52 patients; PD–ICD: 151 patients) 52 post-stroke patients	PD *PD + ICD vs. PD–ICD:* Mean duration: 9.4 ($\pm$0.7) vs. 8.8 ($\pm$0.5) years	DAA, L-dopa, MAO-B inhibitors, entacapone, amantadine *PD + ICD vs. PD–ICD:* LEDD $\geq$1050 mg: 63% vs. 42%	Cross-sectional Case-control	To determine the correlates of ICDs	Age <68 years
Ray et al. [132]	2012	14	14 PD patients: 7 PD with PG 7 PD without PG	PD	Patients withheld DRT for 12 h prior to the PET scans, and were given 1 mg of pramipexole 1 h prior to the scan	Cross-sectional PET coupled with gambling task	To investigate the underlying neurobiology	PD patients with PG have dysfunctional activation of DA autoreceptors in the midbrain and low DA tone in the ACC
Shotbolt et al. [117]	2012	50	50 PD patients with a pre-operative assessment	PD	DBS	Longitudinal	To discuss ICD/DDS and DBS pre-operative and post-operative relationships	*Univariate analysis*: Patients with ICDs and/or DDS: Younger age Male gender
Rana et al. [78]	2013	140	140 PD patients	PD	Amantadine, pramipexole, L-dopa	Retrospective chart review	To determine the correlates of ICDs	5 common variables among the patients who developed ICDs, including male gender
Valença et al. [90]	2013	364	152 PD patients (PD + ICD: 28 patients; PD–ICD: 124 patients) 212 HCs	PD *PD + ICD vs. PD–ICD:* Mean duration: 7.4 ($\pm$4.2) vs. 7.2 ($\pm$5.5) years	Pramipexole, amantadine, selegiline, L-dopa *PD + ICD vs. PD–ICD:* Daily pramipexole dosage = 2.9 ($\pm$1.2) vs. 0.85 ($\pm$1.4) mg LEDD = 732 ($\pm$404) vs. 644 ($\pm$397) mg	Cross-sectional Case-control	To determine the correlates of ICDs	History of smoking

Table 3 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Kim et al. [119]	2013	297	297 PD patients	PD	Stable DRT for at least 3 months	Cross-sectional	To determine the correlates of ICRBs (ICDs, RB and DDS)	*ICDs*: Younger age Higher co-morbid RB and DDS
Bastiaens et al. [68]	2013	46	PD without previous history of ICDs, who were taking a DAA	PD *PD + ICD vs. PD–ICD (baseline):* Mean age at onset (years): 57 (±10) vs. 57 (±9) Mean duration (years): 4 (1–19) vs. 5 (0–14) Motor complications: 61% vs. 25%	DAAs *PD + ICD vs. PD–ICD (follow-up):* Peak DAA-LEDD (mg, median) = 300 (75–450) vs. 165 (50–400)	Longitudinal (4-year prospective cohort study)	To determine the correlates of ICDs	Cigarette smoking Caffeine use Non-significant results: SUD, anxiety, or depression scores
Kim et al. [135]	2013	89	89 PD patients with bilateral STN DBS surgery	PD	Bilateral STN DBS surgery	Longitudinal T1: baseline T2: follow-up (12 months after surgery)	To determine the effect of STN DBS on ICRB	Severity of ICRB worsened more after DBS in older patients
Poletti et al. [97]	2013	805	805 PD patients 593 cognitively preserved 212 demented	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 57 (±12) vs. 66 (±11) Mean duration (years): 10 (±6) vs. 10 (±7)	L-Dopa, DAAs, amantadine, rasagiline	Cross-sectional	To determine the correlates of ICDs	Male gender Younger age

Table 3 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Garcia-Ruiz et al. [92]	2014	233	233 PD patients	PD Mean duration: 5.9 ± 4.1 years	*Oral (n = 197)*: Pramipexole Ropinirole *Transdermal (n = 36)*: Rotigotine	Cross-sectional	To determine the correlates of ICDs	Younger age
Sachdeva et al. [81]	2014	73	73 PD patients: 20 with CSB 11 with ICD with no CSB 42 PD controls	PD *PD + CSB vs. PD + ICD vs. PD–ICD:* Mean duration (months): 96 (±48) vs. 72 (±72) vs. 72 (±66)	*PD + CSB vs. PD + ICD vs. PD–ICD:* LEDD = 941 (±668) vs. 800 (±619) vs. 706 (±693) mg	Cross-sectional Case-control	To determine the correlates of CSB	*PD ± CSB vs. PD controls*: Higher anxiety score *PD ± CSB vs. PD ± ICB and PD controls*: More open to new experiences (NEO–FFI) Less agreeable (NEO–FFI)
Wu et al. [171]	2014	68	29 PD + ICD + PIU 19 PD 20 HCs	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 51.2 (±12) vs. 53.2 (±10) Mean duration (years): 12.4 (±8) vs. 10.4 (±6.2)	*PD + ICD vs. PD–ICD:* DAA-LEDD = 349 (±307) vs. 537 (±329) mg LEDD = 324 (±203) vs. 232 (±329) mg Total LEDD = 673 (±310) vs. 769 (±322) mg	Cross-sectional	To explore Internet use in PD patients with and without ICDs	*PD ± ICD ± PIU:* Higher score in the Y-BOCS-Internet questionnaire
Bancos et al. [74]	2014	147	Group A ($n = 77$): prolactinomas and current/past DAA use Group B ($n = 70$): non-functioning pituitary adenoma and no history of DAA use	Prolactinoma	Cabergoline, bromocriptine	Cross-sectional Postal survey	To determine the correlates of ICDs	Over-representation of males who developed an ICD in group A compared with group B
Callesen et al. [80]	2014	490	490 PD patients	PD	Total LEDD: 555.4 (392.2) mg DAA LEDD: 114.8 (141.9) mg	Cross-sectional	To determine the correlates of ICDs	Younger age More symptoms of depression Higher level of neuroticism Lower levels of agreeableness and conscientiousness

Table 3 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Pontieri et al. [82]	2015	155	155 PD patients: 21 PD + PG 36 PD + ICD-NOS 98 No-ICD	PD *PD + PG vs. PD + ICD-NOS vs. PD-ICD:* Mean age at onset (years): 51 (±8) vs. 57 (±10) vs. 61 (±9) Mean duration (years): 8 (±5) vs. 7 (±4) vs. 5 (±3)	*PD + PG vs. PD + ICD-NOS vs. PD–ICD:* DAA-LEDD = 307 (±275) vs. 316 (±374) vs. 166 (±197) mg LEDD = 487 (±625) vs. 388 (±278) vs. 251 (±279) mg Total LEDD = 794 (±603) vs. 704 (±509) vs. 416 (±303) mg	Study cohort	To determine the correlates of ICDs	*PD patients with PG and with ICD-NOS vs. No-ICD*: Higher severity of psychotic symptoms Higher 'sleep disturbances' and 'sexual preoccupation' scores *PD patients with PG vs. with ICD-NOS and No-ICD*: Younger age Higher severity of depressive and anxious symptoms *PD patients with ICD-NOS vs. No-ICD*: Younger age
Olley et al. [120]	2015	40	40 PD patients: 20 PG_PD 20 NG_PD	PD *PG_PD vs. NG_PD:* Mean age at onset (years): 56.4 (±9) vs. 59.4 (±8) Mean duration (years): 8 (±5) vs. 7.9 (±4)	Cabergoline, pramipexole, pergolide, bromocriptine, L-dopa	Cross-sectional Case-control	To explore the temporal relationships between problem gambling and DRT	Factors influencing/contributing to changes in gambling: Periods of regular premorbid gambling Increased accessibility to gambling venues Ineffective coping skills Mental illness
Tessitore et al. [134]	2015	54	30 PD patients: 15 PD with ICD 15 PD–ICD (matched for age, sex, and educational level) 24 age- and sex-matched HCs	PD *PD + ICD vs. PD–ICD:* Mean duration (years): 5.3 (±3) vs. 6.6 (±4)	*PD + ICD vs. PD–ICD:* DAA-LEDD (mg) = 243 (±82) vs. 243 (±90) Total LEDD (mg) = 477 (±223) vs. 532 (±207)	Cross-sectional Case-control Imaging study in 'on' phase	To determine the correlates of ICDs	*PD patients with ICD vs. without ICD and HC*: Thicker cortex in ACC and OFC Correlation between these structural abnormalities and ICDs severity (and not with cognitive deficits which characterized patients with ICD)

Table 3 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Zainal Abidin et al. [126]	2015	91	91 PD patients: 52 with ICB 39 without ICB	PD *PD + ICB vs. PD–ICB:* Mean duration (years): 8 (±1) vs. 6 (±1)	L-Dopa, DDAs DAA-LEDD (mg) = 83 (±12) vs. 1 (±0.2) LEDD (mg) = 346 (±42) vs. 173 (±27)	Genetic study	To investigate the association of selected polymorphism within the *DRD* and *GRIN2B* genes with the development of ICB	Variants of *DRD1* rs4867798, *DRD1* rs4532, *DRD2/ANKK1* rs1800497, and *GRIN2B* rs7301328
Payer et al. [133]	2015	50	32 PD patients: 11 PD + ICD 21 PD–ICD 18 age-, sex-, and education-matched HCs	PD *PD + ICD vs. PD–ICD:* Mean duration (years): 12 (±4) vs. 7 (±5)	L-Dopa, DAAs (pramipexole, ropinirole, pergolide, amantadine, MAO inhibitors, COMT inhibitors	Cross-sectional Case-control PET study	To investigate the association between ICD in PD and D_3 receptor availability	D_3 receptor levels were not elevated in PD with ICD
Sáez-Francàs et al. [94]	2016	115	115 PD patients: 27 PD with ICD 88 PD without ICD	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 53.7 (±10) vs. 60.3 (±9) Mean duration (months): 74.8 (±49) vs. 46.3 (±42)	DAA, L-dopa, MAO-B inhibitors, amantadine *PD + ICD vs. PD–ICD:* DAA–EDD = 216 (±135) vs. 114 (±135) mg LEDD = 660 (±403) vs. 440 (±521) mg	Cross-sectional	To determine the correlates of ICDs	Higher trait anxiety score Higher impulsivity scores
Vela et al. [95]	2016		87 EOPD patients 87 age- and gender-matched HCs	PD Median disease duration: 5 years	Rasagiline ($n = 48$), L-dopa ($n = 55$) DAAs ($n = 70$): rotigotine, pramipexole, ropinirole, cabergoline	Cross-sectional Case-control	To determine the correlates of ICDs	Higher depression score
Premi et al. [130]	2016	84	84 PD patients: 21 PD + ICD 63 PD–ICD	PD Mean duration: 1.7 ± 2.4 years	Ropinirole, pramipexole, rotigotine, amantadine	Cross-sectional Case-control SPECT imaging	To determine the correlates of ICDs	*PD patients with ICD vs. No-ICD*: Reduction of left putaminal and left inferior frontal gyrus tracer uptake No functional covariance with contralateral basal ganglia and ipsilateral cingulate cortex

Table 3 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Cilia et al. [125]	2016	442	442 PD patients: 154 PD + ICD/DDS 288 PD–ICD/DDS	PD *PD + ICD/DDS vs. PD–ICD/DDS:* Mean duration (years): 8.3 (±5.5) vs. 8.1 (±5.6)	*PD + ICD/DDS vs. PD–ICD/DDS:* DAA-LEDD = 233 (±80) vs. 226 (±88) vs. 166 (±197) mg LEDD = 475 (±291) vs. 456 (±282) mg Total LEDD = 707 (±301) vs. 689 (±302) mg	Cross-sectional Case-control Genotyping AND longitudinal: 2- to 9-year prospective cohort for patients with ICD/DDS only (assessment at 1 year and at the last visit available)	To determine the correlates of ICDs	*PD patients with ICD/DDS vs. No-ICD/DDS:* Association with TPH2 (recessive) and dopamine transporter gene variants (dominant) Association between TPH2 genotype and severity of ICD/DDS *Follow-up*: Association between TPH2 genotype, premorbid depression and higher frequency of depressive symptoms AND more severe behavioral abnormalities, multiple ICDs, and a lower rate of full-remission TPH2 was the strongest predictor of no remission, while the extent of DA agonist daily dose reduction had no effect
Brusa et al. [124]	2016	58	58 PD patients: 37 with PG 21 without PG/ICD	PD	Any dopaminergic medication	Cross-sectional Case-control	To determine the correlates of PG	*PD patients with PG vs. without PG/ICD*: Higher scores on the 3 MMPI-2 validity scales (lying, lying frequency, and defensive behavior) Higher scores on the 2 MMPI-2 content scales (bizarre ideation and cynicism) No significant difference for the clinical scales
Krishnamoorthy et al. [83]	2016	425	170 PD patients: 70 with ICDs 100 No-ICD 285 HCs	PD	L-Dopa (81%) DAAs (pramipexole or ropinirole) (58%)	Cross-sectional Case-control	To determine the correlates of ICDs	*DRD3* p.Ser9Gly (rs6280) heterozygous variant CT

Table 3 continued

Studies	Year	Sample size	Participants	Disease (type, duration, age at onset)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Gescheidt et al. [121]	2016	87	49 EOPD 13 with ICD symptoms 36 without ICD symptoms 38 age-matched HCs	PD Mean duration (years): 11 (3–27)	L-Dopa, DAAs, amantadine, anticholinergics DAA-LEDD (mg) = 300 (105–480) LEDD (mg) = 798 (300–1750) Total LEDD (mg) = 894 (256–2050)	Cross-sectional Case-control	To determine the correlates of ICD symptoms	*PD with ICD symptoms vs. without ICD symptoms (univariate analysis):* Anxiety Somatization Personality style: self-assertive/antisocial and reserved/schizoid Lower conscientiousness in EOPD patients with PG
Smith et al. [129]	2016	320	Untreated PD patients with a DAT imaging deficit at baseline	PD *Baseline characteristics*: Mean disease duration (months): 6.6	*Follow-up characteristics*: L-dopa, DAAs, MAO-B inhibitors, amantadine	Longitudinal (3-year prospective cohort study) DAT SPECT imaging (baseline and follow-up)	To determine the correlates of ICD symptoms	Younger age Lower DAT binding (i.e., greater decrease in DAT availability), ongoing loss over time
Kraemmer et al. [127]	2016	276	PD untreated patients, free of ICD at baseline	PD *Baseline characteristics*: Mean disease duration (months): 6.3 (±6.3)	86% of the patients started DRT during the follow-up 40% of the patients initiated a DAA	Longitudinal (3-year prospective cohort study) Genetic study	To estimate ICD heritability	Heritability = 57% The clinical–genetic prediction model reached highest accuracy *OPRK1*, *HTR2A*, and *DDC* genotypes were the strongest genetic predictive factors
Ramirez Gómez et al. [96]	2017	255	255 PD patients: 70 with ICD 185 No-ICD	PD *PD + ICD vs. PD–ICD:* Median duration (years): 4 vs. 10	DAAs (pramipexole, ropinirole, bromocriptine, piribedil, rotigotine)	Cross-sectional	To determine the correlates of ICDs	Younger age Stimulants use Rapid eye movement sleep disorder behavior

ACC anterior cingulate, *CSB* compulsive sexual behavior, *COMT* catechol-*O*-methyltransferase, *DA* dopamine, *DAA-LEDD* dopamine agonist L-dopa equivalent daily dose, *DAA* dopamine agonist, *DAT* dopamine transporter, *DAWS* dopamine agonist withdrawal syndrome, *DBS* deep-brain stimulation, *DDS* dopamine dysregulation syndrome, *DRT* dopamine replacement therapy, *EOPD* early-onset Parkinson's disease, *HC* healthy control, *ICB* impulsive and compulsive behavior, *ICD* impulse control disorder, *ICD-NOS* impulse control disorder not otherwise specified, *ICRB* impulsive control and repetitive behavior disorders, *L-dopa* levodopa, *LEDD* levodopa equivalent daily dose, *MAO* monoamine oxidase, *MMPI-2* Minnesota Multiphasic Personality Inventory-2, *NEO-FFI* NEO Five-Factor Inventory, *NG_PD* Parkinson's disease without problem gambling, *No-ICD* without impulse control disorder, *OFC* orbitofrontal cortex, *PD* Parkinson's disease, *PET* positron emission tomography, *PG_PD* Parkinson's disease with problem gambling, *PIU* problematic Internet use, *PG* pathological gambling, *RB* repetitive behavior disorder, *RLS* restless legs syndrome, *SPECT* single photon emission computed tomography, *STN* subthalamic nucleus, *SUD* substance use disorder, *Total LEDD* LEDD+DAA-LEDD, *TPH2* tryptophan hydroxylase type 2, *Y-BOCS* Yale–Brown Obsessive Compulsive Scale, + indicates with, − indicates without, ± indicates with or without

Table 4 Disease-related factors

Studies	Year	Sample size	Participants	Disease (duration, type)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Pontone et al. [85]	2006	100	PD patients (PD + ICD: 9 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 44.3 (±9) vs. 48.6 (±9) years Mean duration: 4.6 (±62.2) vs. 6.2 (±5.5) years	Pramipexole, ropinirole, amantadine, entacapone, selegiline, L-dopa *PD + ICD vs. PD–ICD:* L-dopa dose = 627 (±281) vs. 520 (±450) mg	Cross-sectional	To determine the correlates of ICDs	No significant association with PD features (age of onset, duration, stage, UPDRS score, L-dopa dose, etc.)
Giladi et al. [105]	2007	383	193 PD patients (PD + ICD: 27 patients; PD–ICD: 166 patients) 190 age- and gender-matched HC	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 51.5 (±12.2) vs. 58.7 (±12.1) years Mean duration: 10.3 (±4.9) vs. 9.7 (±6.6) years	Ropinirole, pergolide, cabergoline, apomorphine, amandatine, selegiline, entacapone	Cross-sectional	To determine the correlates of ICDs	Younger age at PD motor symptoms onset
Kenangil et al. [101]	2010	554	PD patients (PD + ICD: 33 patients; PD–ICD: 65 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 49 (±9) vs. 52 (±11) Mean duration (years): 8 (±5) vs. 7 (±5)	Pergolide, cabergoline, pramipexole, ropinirole, piribedil, lisuride *PD + ICD vs. PD–ICD:* DAA-LEDD = 369 (±181) vs. 319 (±208) mg Total LEDD = 702 (±2369) vs. 640 (±357) mg	Cross-sectional	To determine the correlates of ICDs	No significant association with severity of PD or presence of L-dopa-induced motor complications
Lee et al. [102]	2010	1167	PG patients	PD Mean age at onset: 58.3 (± 10.5) years Mean duration: 6.6 (± 4.3) years	Stable DRT for at least 3 months Mean duration of DRT: 5.0 (± 3.8) years	Cross-sectional	To determine the correlates of ICRBs	*Univariate analysis*: Longer PD duration Younger age at PD onset Higher frequency of motor complications

Table 4 continued

Studies	Year	Sample size	Participants	Disease (duration, type)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Auyeung et al. [136]	2011	213	PD patients (PD + ICD: 198 patients; PD–ICD: 15 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset: 45.7 (±5.6) vs. 59 (±10.8) years Mean duration: 13.5 (±5.6) vs. 8.9 (±4.8) years	Bromocriptine, ropinirole, pramipexole, rotigotine, L-dopa *PD + ICD vs. PD–ICD:* DAA-LEDD = 277 (±147) vs. 85 (±98) mg Total LEDD = 1215 (±635) vs. 634 (±330) mg	Cross-sectional	To determine the correlates of ICDs	Younger age at PD onset
Voon et al. [122]	2011	564	564 PD patients: 282 with ICDs 282 No-ICD (matching on age, gender, and DAA treatment)	PD	DAAs ± L-dopa	Cross-sectional Case-control *(DOMINION study)*	To determine the correlates of ICDs	More functional impairment Decreased motivation
Voon et al. [70]	2011	140	RLS ± ICD	RLS	DAAs (ropinirole 2–4.5 mg/day: $n = 3$; pramipexole 0.72–1.4 mg/day: $n = 3$; lisuride 2.5 mg/day: $n = 1$; cabergoline 3 mg/day: $n = 1$) L-dopa (100 mg/d: $n = 3$)	Cross-sectional	To determine the correlates of ICDs	Younger age at RLS onset (46.6 [SD = 10.1] vs. 57 [15.9] years)
Hassan et al. [106]	2011	321	DAA-treated PD patients	PD	Ropinirole and pramipexole, L-dopa, selegiline, rasagiline, amantadine, entacapone	Cohort (retrospective)	To determine the correlates of ICDs	*Univariate analysis*: Younger age at PD onset (51 vs. 59 years)
Lim et al. [137]	2011	200	200 PD patients	PD	Piribedil, pramipexole, ropinirole, bromocriptine, amantadine Low dosages of DRT	Cross-sectional	To determine the correlates of ICDs	Longer PD duration

Table 4 continued

Studies	Year	Sample size	Participants	Disease (duration, type)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Solla et al. [75]	2011	349	349 PD patients: 87 without MC 262 with MC	PD *PD + MC vs. PD–MC:* Mean age at onset (years): 62 (±10) vs. 63 (±10) Mean duration (years): 11 (±6) vs. 6 (±6)	L-Dopa, DAAs *PD + MC vs. PD–MC:* DAA-LEDD (mg) = 73 (±106) vs. 64 (±79) Total LEDD (mg) = 606 (±324) vs. 411 (±238)	Cross-sectional	To determine the correlates of motor complications	Higher frequency of ICDs in patients with MC (12.2%) than in patients without MC (3.4%)
Vallelunga et al. [168]	2011	89	89 PD patients: 48 No-ICD 41 with ICDs	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 53 (±10) vs. 57 (±11) Mean duration (years): 9 (±4) vs. 11 (±8)	*PD + ICD vs. PD–ICD:* DAA use: 40/41 vs. 38/48 DAA-LEDD = 168 (±114) vs. 124 (±114) mg	Cross-sectional Case-control	To determine the correlates of ICDs	*Univariate analysis*: Younger age at PD onset
Limotai et al. [77]	2012	1 040	PD patients, excluding those who were never exposed to DAA (PD + ICD: 89 patients; PD–ICD: 951 patients)	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 52 (±10) vs. 60 (±12) Mean duration (years): 12 (±6) vs. 11 (±7)	*PD + ICD vs. PD–ICD:* LEDD = 971 (±663) vs. 672 (±512) mg DAA-LEDD = 292 (±184) vs. 142 (±176) mg Total LEDD = 1122 (±644) vs. 779 (±543) mg	Retrospective (cohort)	To determine the correlates of DAWS, DDS, and ICDs	*Univariate analysis concerning ICDs*: Younger age at PD onset
Leroi et al. [76]	2012	99	99 PD patients: 35 PD + ICD 26 PD + apathy 38 control PD	PD	57.6% were taking DRT	Cross-sectional Case-control	To determine the correlates of ICDs and apathy	*Univariate analysis*: PD + ICD vs. PD + apathy Younger age at PD onset Greater motor disease complexity.

Table 4 continued

Studies	Year	Sample size	Participants	Disease (duration, type)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Aarts et al. [140]	2012	58	32 PD patients: 10 never-medicated 22 after DA medication washout 26 HCs	PD Mean duration (years): 4 (±2)	L-Dopa, DAAs, MAO-B inhibitors	Cross-sectional with a within- and between-subjects design SPECT coupled with rewarded task-switching paradigm	To investigate the underlying neurobiology	Relation between aberrant reward processing and DA depletion in the striatum, but not long-term DA medication use Relation between the aberrant reward processing and the degree of DA cell loss
Bastiaens et al. [68]	2013	46	PD without previous history of ICDs, who were taking a DAA	PD *PD + ICD vs. PD–ICD (baseline):* Mean age at onset (years): 57 (±10) vs. 57 (±9) Mean duration (years): 4 (1–19) vs. 5 (0–14) Motor complications: 61 vs. 25%	DAAs *PD + ICD vs. PD–ICD (follow-up):* Peak DAA-LEDD (mg, median) = 300 (75–450) vs. 165 (50–400)	Longitudinal (4-year prospective cohort study)	To determine the correlates of ICDs	Motor complications Higher MMSE scores Non-significant results: PD duration
Rana et al. [78]	2013	140	140 PD patients	PD	Amantadine, pramipexole, L-dopa	Retrospective chart review	To determine the correlates of ICDs	5 common variables among the patients who developed ICDs, including: Stage 1–2 of PD Young age at PD onset
Kim et al. [135]	2013	89	89 PD patients with bilateral STN DBS surgery	PD	Bilateral STN DBS surgery	Longitudinal T1: baseline T2: follow-up (12 months after surgery)	To determine the effect of STN DBS on ICRB	Younger age at PD onset was associated with a larger increase in MIDI scores in patients with ICRB (before or after surgery)
Callesen et al. [80]	2014	490	490 PD patients	PD	Total LEDD: 555.4 (392.2) mg DAA LEDD: 114.8 (141.9) mg	Cross-sectional	To determine the correlates of ICDs	Younger age at PD onset Longer PD duration More motor symptoms

Table 4 continued

Studies	Year	Sample size	Participants	Disease (duration, type)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Rodríguez-Violante et al. [93]	2014	450	300 PD patients (PD + ICD: 77 patients; PD–ICD: 223 patients) 150 HCs (including 25 patients)	PD	L-Dopa, DAAs (especially pramipexole), amantadine *PD + ICD vs. PD–ICD:* DAA-LEDD (mg) = 147 (±123) vs. 97 (±125) LEDD (mg) = 638 (±449) vs. 561 (±417)	Cross-sectional Case-control	To determine the correlates of ICDs	Motor fluctuations Higher score on MDS-UPDRS part 1
Harris et al. [138]	2015	82	38 PD patients: 19 right onset 19 left onset 44 HCs	PD	L-Dopa, DAAs, anticholinergic, COMT, MAO inhibitor *Right onset vs. left onset:* LEDD (mg) = 423 (±246) vs. 453 (±271)	Cross-sectional Case-control	To determine the correlates of side of onset of PD	*Right-onset PD vs. left-onset PD*: Higher levels of novelty seeking
Al-Khaled et al. [139]	2015	83	37 PD (13 never-medicated and 24 medicated) 24 RLS 22 HCs	PD and RLS *PD + medicated vs. PD–medicated vs. RLS:* Mean duration (years): 6 (±4) vs. 2 (±1) vs. 14 (±12)	*PD + medicated vs. PD–medicated vs. RLS:* DAA-LEDD (mg) = 159 (±118) vs. 0 vs. 66 (±69) Total LEDD (mg) = 440 (±247) vs. 0 vs. 123 (±99)	Cross-sectional with a between-subjects design Delay discounting task	To investigate the underlying neurobiology	Never-medicated PD patients had a higher discounting rate than HCs and medicated RLS patients Impulsive decision-making in PD patients may not be a side effect of DA treatment, but rather a trait marker of PD
Pontieri et al. [82]	2015	155	155 PD patients: 21 PD with PG 36 PD with ICD-NOS 98 No-ICD	PD *PD + PG vs. PD + ICD-NOS vs. PD-ICD:* Mean age at onset (years): 51 (±8) vs. 57 (±10) vs. 61 (±9) Mean duration (years): 8 (±5) vs. 7 (±4) vs. 5 (±3)	*PD + PG vs. PD + ICD-NOS vs. PD-ICD:* DAA-LEDD = 307 (±275) vs. 316 (±374) vs. 166 (±197) mg LEDD = 487 (±625) vs. 388 (±278) vs. 251 (±279) mg Total LEDD = 794 (±603) vs. 704 (±509) vs. 416 (±303) mg	Study cohort	To determine the correlates of ICDs	*PD patients with PG and with ICD-NOS vs No-ICD*: Longer PD duration *PD patients with PG vs. with ICD-NOS and No-ICD*: Younger age at PD onset *PD patients with ICD-NOS vs. No-ICD*: Younger age at PD onset

Table 4 continued

Studies	Year	Sample size	Participants	Disease (duration, type)	DA drug (molecule, dosage, duration)	Design	Objectives	Main results
Sáez-Francàs et al. [94]	2016	115	115 PD patients: 27 PD with ICD 88 PD without ICD	PD *PD + ICD vs. PD–ICD:* Mean age at onset (years): 53.7 (±10) vs. 60.3 (±9) Mean duration (months): 74.8 (±49) vs. 46.3 (±42)	DAA, L-dopa, MAO-B inhibitors, amantadine *PD + ICD vs. PD–ICD:* DAA-LEDD = 216 (±135) vs. 114 (±135) mg LEDD = 660 (±403) vs. 440 (±521) mg	Cross-sectional	To determine the correlates of ICDs	Younger age at PD onset Higher score on the UPDRS-I subscale
Krishnamoorthy et al. [83]	2016	455	170 PD patients: 70 with ICDs 100 No-ICD 285 HCs	PD	L-Dopa (81%) DAAs (pramipexole or ropinirole) (58%)	Cross-sectional Case-control	To determine the correlates of ICDs	Age at PD onset <50 years
Ramirez Gómez et al. [96]	2017	255	255 PD patients: 70 with ICD 185 No-ICD	PD *PD + ICD vs. PD-ICD:* Median duration (years): 4 vs. 10	DAAs (pramipexole, ropinirole, bromocriptine, piribedil, rotigotine)	Cross-sectional	To determine the correlates of ICDs	*Negative association*: Presence of dyskinesias and motor fluctuations

COMT catechol-*O*-methyltransferase, *DA* dopamine, *DAA-LEDD* dopamine agonist L-dopa equivalent daily dose, *DAA* dopamine agonist, *DAWS* dopamine agonist withdrawal syndrome; *DBS* deep-brain stimulation, *DDS* dopamine dysregulation syndrome, *DRT* dopamine replacement therapy, *HC* healthy control, *ICD* impulse control disorder, *ICD-NOS* impulse control disorder not otherwise specified, *ICRB* impulsive control and repetitive behavior disorders, *L-dopa* levodopa, *LEDD* levodopa equivalent daily dose, *MAO inhibitor* monoamine oxydase inhibitor, *MC* motor complications, *MDS-UPDRS* Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale, *MIDI* Minnesota Impulsive Disorders Interview, *MMSE* Mini-Mental State Examination, *No-ICD* without impulse control disorder, *PD* Parkinson's disease, *PG* pathological gambling, *RLS* restless legs syndrome, *SD* standard deviation, *SPECT* single photon emission computed tomography, *STN* subthalamic nucleus, *Total LEDD* LEDD+DAA-LEDD, *UPDRS* Unified Parkinson's Disease Rating Scale, + indicates with, − indicates without

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