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.

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 D2/3 over D1 receptors. Lisuride acts specifically on D2 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 D2/3 selective and thus better tolerated [1]. These two drugs have a highly specific affinity to cerebral D3 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 D1 receptors as compared to D2 receptors. Apomorphine, which has approximately equal affinities for D2 and D3 [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 hobbies, punting, 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 Manual 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

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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].
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 D₃ 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

3.3.3.1 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].

D₂ receptor availability was no different between PD patients with or without ICDs at baseline, but a greater reduction of ventral striatum ¹¹C-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 D₃ 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 D3 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 D3 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 D3 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 oxidase 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

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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 D3 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 pre-morbid 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
| 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                                     | Pramipexole, ropinirole, amantadine, entacapone, selegiline, l-dopa | Cross-sectional | To determine the frequency of ICDs  | Prevalence = 9% (n = 9) ICDs: gambling (4%) = sexuality (4%) > spending (3%) |
|                          |      |             |                                        | PD + ICD vs. PD–ICD:                    |                                       |                 |                                       |                                                                                |
|                          |      |             |                                        | Mean age at onset (years): 44.3 (±9) vs. 48.6 (±9) |                                       |                 |                                       |                                                                                |
|                          |      |             |                                        | Mean duration (years): 4.6 (±6.2) vs. 6.2 (±5.5) |                                       |                 |                                       |                                                                                |
| 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) |
| Voon et al. [10]         | 2006 | 297         | PD patients                            | PD + PG vs. PD + HS vs. PD + CS vs. PD–ICD: | l-Dopa, DAA, pramipexole, ropinirole. | Cross-sectional | 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 |
| Studies            | Year | Sample size | Sample 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                                       | Ropinirole, pergolide, cabergoline, apomorphine, amantadine, 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) | 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 Carbipodap-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 carbipodap-L-dopa or a DAA at subtherapeutic doses |
| 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                  | 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):  | Cross-sectional                  | To determine the frequency of ICDs  | Prevalence = 13.6% (3.9% with ≥ 2 ICDs)                                       |
|                         |      |             |                                    | Pramipexole: 3.1 mg (SD = 1.7) and 306.9 mg (SD = 168.2); |                                      | Case-control (matching on age, sex and DAA treatment) | (DOMINION study) | ICDs: shopping (5.7%) > gambling (5%) > eating (4.3%) > sexuality (3.5%)       |
|                         |      |             |                                    | 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) |                                      |                                  |                                    |                                                                                |
| Lee et al. [102]        | 2010 | 1167        | PG patients                        | PD                                    | Stable DRT for at least 3 months     | Cross-sectional                  | To determine the frequency of ICRBs | Prevalence = 10.1%                                                              |
|                         |      |             |                                    | Mean age at onset (years): 58 (±11)   |                                      |                                  |                                    | ICRBs: punding (4.2%) > eating (3.4%) > sexuality (2.8%) > shopping (2.5%) > gambling (1.3%) |
|                         |      |             |                                    | Mean duration (years): 7 (±4)         |                                      |                                  |                                    |                                                                                |
| Kenangil et al. [101]   | 2010 | 554         | PD patients (PD + ICD: 33 patients; PD – ICD: 65 patients) | PD                                    | Pergolide, cabergoline, pramipexole, ropinirole, piribedil, lisuride | Cross-sectional                  | To determine the frequency of ICDs  | Prevalence = 5.9%                                                              |
|                         |      |             |                                    | Mean age at onset (years): 49 (±9) vs. 52 (±11) |                                      |                                  |                                    | ICDs: punding (57%) > sexuality (42%) > eating (27%) > shopping (24%)          |
|                         |      |             |                                    | Mean duration (years): 8 (±5) vs. 7 (±5) |                                      |                                  |                                    |                                                                                |
| Studies            | Year | Sample size | Participants                                                                                           | Disease (type, duration, age at onset) | DA drug (molecule, dosage, duration) | Design                     | Objectives                  | Main results                                                                 |
|-------------------|------|-------------|--------------------------------------------------------------------------------------------------------|----------------------------------------|---------------------------------------|----------------------------|----------------------------|--------------------------------------------------------------------------------|
| Pourcher et al.   | 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.     | 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. | 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.    | 2011 | 213         | PD patients (PD + ICD: 198 patients; PD-ICD: 15 patients)                                                                 | PD                                     | Bromocriptine, ropinirole, pramipexole, rotigotine, l-dopa | Cross-sectional | To determine the frequency of ICDs | Prevalence = 7% |
| Studies            | Year | Sample size | Participants | Disease (type, duration, age at onset) | DA drug (molecule, dosage, duration) | Design            | Objectives                                                                 | Main results                                                                 |
|-------------------|------|-------------|--------------|----------------------------------------|--------------------------------------|------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Zahodne et al.    | 2011 | 96          | 96 PD patients (PD + BED: 9 patients; PD–BED: 87 patients) | PD                                     | DAA                                  | 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.       | 2011 | 140         | RLS          | 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) | 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.        | 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%) |
| 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: LEDD = 971 (±663) vs. 672 (±512) mg DAA-LEDD = 292 (±184) vs. 142 (±176) mg Total LLED = 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               | 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) | PD                                     | PD + ICD vs. PD–ICD: LEDD ≥1050 mg: 63% vs. 42% | Cross-sectional               | 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) | PD                                     | Pramipexole, amantadine, selegiline, L-dopa | Cross-sectional               | 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) |
| Studies            | Year | Sample size | Participant details                        | 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                    | 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                                     | DAAs                                  | 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                     | 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 |
| 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        | PD                                     | l-Dopa, DAAs, amantadine, rasagiline | Cross-sectional| To determine the frequency of ICDs       | Prevalence = 39.1%                                    |
|                   |      |             | 593 cognitively preserved | PD + ICD vs. PD–ICD: <br> Mean age at onset (years): 57 (±12) vs. 66 (±11) <br> Mean duration (years): 10 (±6) vs. 10 (±7) | | | | Prevalence in cognitively preserved PD patients = 9.6% <br> Prevalence in demented PD patients = 3.8% |
| Bancos et al. [74] | 2014 | 147         | Group A (n = 77): prolactinomas and current/past DAA use <br> 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 <br> DAA: 114.8 (141.9) mg | Cross-sectional| To determine the frequency of ICDs       | Prevalence = 35.9% (lifetime)/ 14.9% (current) |
| Rodriguez-Violante et al. [93] | 2014 | 450         | 300 PD patients <br> (PD + ICD: 77 patients; PD–ICD: 223 patients) <br> 150 healthy controls (including 25 patients) | PD                                     | l-Dopa, DAAs (especially pramipexole), amantadine <br> PD + ICD vs. PD–ICD: DA-LEDD (mg) = 147 (±123) vs. 97 (±125) <br> LEDD (mg) = 638 (±449) vs. 561 (±417) | Cross-sectional | Case-control | To determine the frequency of ICDs | Prevalence = 10.6% (5.3% in HC) <br> 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                                     | Oral (n = 197): Pramipexole <br> Ropinirole <br> Transdermal (n = 36): Rotigotine | Cross-sectional | To determine the frequency of ICDs       | Prevalence = 39.1%                                   |
| 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: 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                                      | 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                                      | 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 |
| 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                                       | Rasagiline ($n = 48$), l-dopa ($n = 55$) DAAs ($n = 70$): rotigotine, pramipexole, ropinirole, cabergoline | Cross-sectional     | 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                                       | l-Dopa, DAAs, amantadine, anticholinergics DAA-LEDD (mg) = 300 (105–480) LEDD (mg) = 798 (300–1750) Total LEDD (mg) = 894 (256–2050) | Cross-sectional     | 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                                       | 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 having a DAT imaging deficit at baseline              | PD                                       | Follow-up characteristics: l-dopa, DAAs, MAO-B inhibitors, amantadine Mean disease duration (months): 6.6 | 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 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 |
| Antonini et al. [107] | 2016 | 786         | PD patients treated by rotigotine transdermal patch                         | PD                                       | Rotigotine Duration of exposure (months): 49 (±18) | Post hoc analysis of 6 open-label extension studies | To determine the incidence of ICDs | |
| Studies          | Year | Sample size | Participants | Disease (type, duration, age at onset) | DA drug (molecule, dosage, duration) | Design | Objectives | Main results       |
|------------------|------|-------------|--------------|----------------------------------------|--------------------------------------|--------|-------------|---------------------|
| Kraemmer et al.  | 2016 | 276         | PD untreated patients, free of ICD at baseline | PD                                     | 86% of the patients started DRT during the follow-up | 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                                     | 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
| 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                                     | Pramipexole, ropinirole, amantadine, entacapone, selegiline, l-dopa          | 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 | 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) | PD                                     | Ropinirole, pergolide, cabergoline, apomorphine, amantadine, 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 |
| 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                                     | Pramipexole, ropinirole, cabergoline                      | Crossover (‘on’ and ‘off’ DAA medication)            | 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  | PD PD + ICD vs. PD–ICD: Mean age at onset (years): 59 (±7) vs. 60 (±11) | l-dopa, piribedil, pramipexole, amantadine, pergolide, ergocriptine, bromocriptine PD + ICD vs. PD–ICD: Mean duration (years): 5 (±3) vs. 6 (±3) | Cross-sectional                                    | To determine the correlates of ICDs                                             | DAA use                                                                                                                                                                                                      |
| van Eimeren et al. [110]      | 2009 | 8           | PD patients                                                                  | Patients with early-stage PD            | 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). |                                                                                                                                                                                                             |
| Studies            | Year | Sample size | Participants | Disease (duration, type, age at onset) | DA drug (molecule, dosage, duration) | Design                          | Objectives                          | Main results                        |
|--------------------|------|-------------|---------------|----------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|-------------------------------------|
| Kenangil et al.    | 2010 | 554         | PD patients   | PD                                     | Pergolide, cabergoline, pramipexole, ropinirole, pinbedil, lisuride | Cross-sectional                  | To determine the correlates of ICDs | No association between ICDs and doses of DAAs |
|                    |      |             | (PD + ICD: 33 patients; PD–ICD: 65 patients) | PD + ICD vs. PD–ICD: Mean age at onset (years): 49 (±9) vs. 52 (±11) Mean duration (years): 8 (±5) vs. 7 (±5) | PD + ICD vs. PD–ICD: DAA-LEDD (mg) = 369 (±181) vs. 319 (±208) Total LEDD (mg) = 702 (±2369) vs. 640 (±357) |                                  |                                     |
| Weintraub et al.   | 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                                     | 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 |
|                    |      |             |               | PD                                     |                                    |                                  |                                     | 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 |
| Voon et al. [112]  | 2010 | 44          | 14 PD + ICD patients | 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) | Crossover with a within- and between-subjects design (‘on’ and ‘off’ DAA medication) | To investigate the underlying neurobiology |                                     |
| Studies            | Year | Sample size | Participants | Disease (duration, type, age at onset) | DA drug (molecule, dosage, duration) | Design | Objectives | Main results |
|--------------------|------|-------------|--------------|----------------------------------------|----------------------------------------|--------|------------|--------------|
| Pallanti et al.    | 2010 | 24          | 24 PD patients who underwent STN DBS | PD                                     | STN DBS                                | Cross-sectional | To investigate the underlying neurobiology | Non-punders: started bilateral STN DBS on average 1.96 years before the punders |
| Sohtaoglu et al.   | 2010 | 22          | 22 PD patients with ICDs | PD                                     | DAA (mg/day) = 3.7 (±1.7) l-dopa (mg/day) = 239 (±252) | Longitudinal | To evaluate the outcome of ICDs | Recovery from compulsive behaviors after reducing dosage of DAAs for 16/22 patients |
| Voon et al.        | 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.        | 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]) |
| 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                                  | Bromocriptine, ropinirole, pramipexole, rotigotine, L-dopa | 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                                  | Pramipexole, ropinirole, pergolide, cabergoline, rotigotine | Longitudinal | 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          | PD patients (PD + BED: 9 patients; PD–BED: 87 patients) | PD                                  | DAA STN DBS surgery | Cross-sectional | To determine the correlates of BED and subthreshold BED | History of DBS No significant association with DAAs |
| 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 L-Dopa, DAAs | 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: 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: 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 |
| 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                                     | 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                                     | 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                                     | 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 ICD: No significant association with DAAs doses | 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 ICD: No significant association with DAAs doses |
| 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: 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, 1-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:  
Pramipexole, amantadine, selegiline, l-dopa  
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 |
| 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                  | 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                                     | DAAs                                 | 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                  | 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. |
| Studies         | Year | Sample size | Participants | Disease (duration, type, age at onset) | DA drug (molecule, dosage, duration) | Design | Objectives | Main results |
|-----------------|------|-------------|--------------|----------------------------------------|-------------------------------------|--------|------------|--------------|
| Sharp et al.    | 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 | 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 |
| [169]           |      |             |              |                                        |                                     |        |            |              |
| Poletti et al.  | 2013 | 805         | 805 PD patients 593 cognitively preserved 212 demented | PD | L-Dopa, DAAs, amantadine, rasagiline | Cross-sectional | To determine the correlates of ICDs | DAA use (no difference between pramipexole and ropinirole) L-dopa use |
| [97]            |      |             |              |                                        |                                     |        |            |              |
| Callesen et al. | 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) |
| [80]            |      |             |              |                                        |                                     |        |            |              |
| Moore et al.    | 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 D3 receptor). |
| [91]            |      |             |              |                                        |                                     |        |            |              |
| Studies          | Year | Sample size | Participants                                                                 | Disease (duration, type, age at onset) | DA drug (molecule, dosage, duration) | Design                      | Objectives                              | Main results                             |
|------------------|------|-------------|-------------------------------------------------------------------------------|----------------------------------------|--------------------------------------|-----------------------------|-----------------------------------------|------------------------------------------|
| Sachdeva et al.  | 2014 | 73          | 73 PD patients: 20 with CSB, 11 with ICD–CSB, 42 PD controls                  | PD                                     | PD + CSB vs. PD + ICD vs. PD–ICD: LEDD = 941 (±668) vs. 800 (±619) vs. 706 (±693) mg | Cross-sectional            | To determine the correlates of CSB      | PD ± CSB vs. PD controls: Higher LEDD |
|                  |      |             |                                                                               |                                        |                                      | Case-control               |                          |                                           |
|                  |      |             |                                                                               |                                        |                                      |                            |                          |                                           |
| Garcia-Ruiz et al. [92] | 2014 | 233         | 233 PD patients                                                               | PD                                     | 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            | 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 |
|                  |      |             |                                                                               |                                        |                                      |                            |                          |                                           |
| Rodriguez-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 | Cross-sectional            | To determine the correlates of ICDs     | DAA use: Higher DAA-LEDD               |
|                  |      |             |                                                                               |                                        |                                      |                            |                          |                                           |
| 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                                     | 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 |
| 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 |
| 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: 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 |
| 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                                     | 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          | 87 EOPD patients 87 age- and gender-matched HCs | PD                                     | Rasagiline (n = 48), L-dopa (n = 55) DAAs (n = 70): rotigotine, pramipexole, ropinirole, cabergoline | Cross-sectional | To determine the correlates of ICDs                      | DAA use                                           |
| Chang et al. [170]          | 2016 | 15          | 15 PD patients treated with LCIG | PD                                     | Intradaudenal LCIG infusion during 16 h/day for 6 months Stop DA agonists: oral L-dopa/carbidopa authorized for nocturnal ‘off’ symptoms | Longitudinal | 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 |
| 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                                     | 1-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) | 1-Dopa, DAAs, amantadine, anticholinergics | 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 Median duration (years): 4 vs. 10 | DAAs (pramipexole, ropinirole, bromocriptine, piribedil, rotigotine) | Cross-sectional | To determine the correlates of ICDs | DDA 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.
| 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                                                                           | Pramipexole, ropinirole, amantadine, entacapone, selegiline, 1-dopa | Cross-sectional                      | To determine the correlates of ICDs | Discrete symptoms of depressed mood, irritability, appetite changes, and disinhibition |
| Giladi et al. [105]     | 2007 | 383 PD patients (PD + ICD: 27 patients; PD–ICD: 166 patients) 190 age- and gender-matched HCs | PD                                                                           | Ropinirole, pergolide, cabergoline, apomorphine, amantadine, 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, 1-dopa | 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                                                                           | L-Dopa, piribedil, pramipexole, amantadine, pergolide, ergocriptine, bromocriptine | Cross-sectional                      | To determine the correlates of ICDs | Alcohol daily use                                                                |
| 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 \(n = 3031\)      | Cross-sectional | To determine the correlates of ICDs   | Living in the USA                                   |
|                               |      |             |                                       |                                        | DAAs (mean daily dosage and LEDDs):  |         |                                     | Younger age                                        |
|                               |      |             |                                       |                                        | Pramipexole 3.1 (±1.7) and 306.9 (±168.2) mg |         |                                     | Being unmarried                                     |
|                               |      |             |                                       |                                        | Ropinirole: 11.1 (±6.6) and 277.9 (±164.9) mg |         |                                     | Current nicotine use                                |
|                               |      |             |                                       |                                        | Pergolide: 2.9 (±1.7) and 286.6 (±169.3) mg |         |                                     | Family history of gambling problems                |
| Cilia et al. [128]            | 2010 | 43          | 29 PD patients: 8 PD with PG          | PD                                     | l-Dopa + DAAs                         | Cross-sectional | To investigate the underlying neurobiology | DAT density differed between the 3 groups in both dorsal and ventral striata bilaterally |
|                               |      |             | 21 PD–ICD (matched for demographic, clinical features, and mean daily DRT intake) | PD + PG vs. PD–ICD: Mean duration: 6 (±2) vs. 6 (±2) years | PD + PG vs. PD–ICD: Total LEDD \(\text{mg} = 831 (±294) \text{vs.} 852 (±301)\) |         |                                     | Post hoc analysis: reduced tracer binding in the ventral striatum for PD with PG compared to PD without ICD |
|                               |      |             | 14 HCs                                | PD                                     | DAA-LLED \(\text{mg} = 241 (±118) \text{vs.} 252 (±121)\) | Cross-sectional | Imaging study (SPECT of DAT) |                                                   |
| Lee et al. [102]              | 2010 | 1167        | PG patients                           | PD                                     | Stable DRT for at least 3 months     | Cross-sectional | To determine the correlates of ICRBs      | Univariate analysis: male gender for gambling and sexuality |
|                               |      |             |                                       | Mean age at onset: 58.3 (±10.5) years | Mean duration of DRT: 5.0 years (±3.8) |         |                                     |                                                   |
|                               |      |             |                                       | Mean duration: 6.6 (±4.3) years       |                                         |         |                                     |                                                   |
| Pourcher et al. [123]         | 2010 | 97          | 97 RLS patients: 32 untreated patients without compulsions | RLS                                     | Stable DAA (average dose 0.52 mg pramipexole equivalent) | Longitudinal | To determine the correlates of motor/behavioral compulsions | More stress, depression, and sleep problems          |
|                               |      |             | 53 DAA-treated patients without compulsions |                                          |                                         | T1: baseline |                                                   |                                                   |
|                               |      |             | 12 DAA-treated patients with compulsions |                                          |                                         | T2: 4 months |                                                   |                                                   |
|                               |      |             |                                       |                                          |                                         | T3: 8 months |                                                   |                                                   |
| 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                                    | DAAAs (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                                    | Bromocriptine, pramipexole, ropinirole, rotigotine, l-dopa | 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 | 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           | PD                                     | PD + ICD vs. PD–ICD: DAA use: 40/41 vs. 38/48 | Cross-sectional Case-control study | To determine the correlates of ICDs | Univariate analysis: Younger age     |
|                               |      |             | 41 with ICD                         |                                        | DAA-Ledd = 168 (±114) vs. 124 (±114) mg |            |                                   |                                    |
|                               |      |             |                                    |                                        | 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 |            |                                   |                                    |
| O’Sullivan et al. [131]       | 2011 | 18          | 18 PD patients; 7 No-ICD            | PD                                     | PD + ICD vs. PD–ICD: DAA-Ledd = 62 (±92) vs. 241 (±143) mg | Cross-sectional Case-control study 3 11C-raclopride PET scans | To determine the correlates of ICDs | PD patients with ICDs vs. without: |
|                               |      |             | 11 with ICD                         |                                        | Ledd = 636 (±325) vs. 708 (±319) mg |            |                                   | No significant differences in baseline dopamine D2 receptor availability |
|                               |      |             |                                    |                                        | Mean age at onset: 45.1 (±11.2) vs. 47 (±8.8) years |            |                                   | Greater reduction of ventral striatum 11C-raclopride binding potential following reward-related cue exposure, relative to neutral cue exposure, following l-dopa challenge |
|                               |      |             |                                    |                                        | Mean duration: 11.9 (±11.3) vs. 10.7 (±6.4) years |            |                                   |                                    |
| 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: Ledd = 971 (±663) vs. 672 (±512) mg | Retrospective (cohort) | To determine the correlates of DAWS, DDS, and ICDs | Univariate analysis concerning ICDs: Male gender Younger age |
|                               |      |             |                                    |                                        | DAA-Ledd = 292 (±184) vs. 142 (±176) mg |            |                                   |                                    |
|                               |      |             |                                    |                                        | Total Ledd = 1122 (±644) vs. 779 (±543) mg |            |                                   |                                    |
|                               |      |             |                                    |                                        | Mean age at onset: 52 (±10) vs. 59.7 (±12) years |            |                                   |                                    |
|                               |      |             |                                    |                                        | Mean duration: 11.5 (±6.1) vs. 11.3 (±6.8) years |            |                                   |                                    |
| Leroi et al. [76]             | 2012 | 99          | 99 PD patients; 35 PD + ICD         | 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. |
|                               |      |             | 26 PD + apathy                      |                                        |                                      |            |                                   |                                    |
|                               |      |             | 38 control PD                       |                                        |                                      |            |                                   |                                    |
| 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                                      | DAA, L-dopa, MAO-B inhibitor           | Longitudinal            | T1: baseline T2: follow-up (15 months later)         | 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         | To determine the correlates of ICDs                  | Higher depression score Male gender Age ≤65 years Age <68 years |
| Perez-Lloret et al. [103] | 2012 | 255         | 203 PD patients (PD + ICD: 52 patients; PD–ICD: 151 patients), 52 post-stroke patients | PD                                      | DAA, L-dopa, MAO-B inhibitors, entacapone, amantadine | Cross-sectional Case-control | To determine the correlates of ICDs                  | PD patients with PG have dysfunctional activation of DA autoreceptors in the midbrain and low DA tone in the ACC |
| 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                                      | Pramipexole, amantadine, selegiline, L-dopa | Cross-sectional Case-control | To determine the correlates of ICDs                  | History of smoking |
| 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                                     | DAAs                                | 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 | PD                                     | 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: | PD | 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 | 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 | PD | Mean age at onset (years): 51.2 (±12) vs. 53.2 (±10) | 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 | Prolactinoma | | Cabergoline, bromocriptine | Cross-sectional | 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 |
| 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:                                  | PD                                     | PD + PG vs. PD + ICD-NOS vs. PD–ICD: | Study cohort | To determine the correlates of ICDs                                        | PD patients with PG and with ICD-NOS vs. No-ICD: Higher severity of psychotic symptoms   |
|                         |      |             | 21 PD + PG                                        |                                        | DAA-LEDD = 307 (±275) vs. 316 (±374) vs. 166 (±197) mg |            |                                                                             | Higher ‘sleep disturbances’ and ‘sexual preoccupation’ scores                        |
|                         |      |             | 36 PD + ICD-NOS                                   |                                        | 388 (±278) vs. 251 (±279) mg            |            |                                                                             | PD patients with PG vs. with ICD-NOS and No-ICD: Younger age                              |
|                         |      |             | 98 No-ICD                                         |                                        | Total LEDD = 394 (±603) vs. 704 (±509) vs. 416 (±303) mg |            |                                                                             | Higher severity of depressive and anxious symptoms                                       |
|                         |      |             | PD                                                 |                                        | Mean age at onset (years): 51 (±8) vs. 57 (±10) vs. 61 (±9) |            |                                                                             | PD patients with ICD-NOS vs. No-ICD:                                                      |
|                         |      |             | PG vs. PD                                         |                                        | Mean duration (years): 8 (±5) vs. 7 (±4) vs. 5 (±3) |            |                                                                             | Younger age                                                                                |
| Olley et al. [120]      | 2015 | 40          | 40 PD patients:                                   | PD                                     | Cabergoline, pramipexole, pergolide, bromocriptine, l-dopa | Cross-sectional | 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 |
|                         |      |             | 20 PG_PD                                          |                                        | Mean age at onset (years): 56.4 (±9) vs. 59.4 (±8) |            |                                                                             | PD patients with ICD-NOS vs. No-ICD:                                                      |
|                         |      |             | 20 NG_PD                                          |                                        | Mean duration (years): 8 (±5) vs. 7.9 (±4) |            |                                                                             | Younger age                                                                                |
| Tessitore et al. [134]  | 2015 | 54          | 30 PD patients:                                   | PD                                     | PD + ICD vs. PD–ICD: DAA-LEDD (mg) = 243 (±82) vs. 243 (±90) | Cross-sectional | 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) |
|                         |      |             | 15 PD with ICD                                    |                                        | Mean duration (years): 5.3 (±3) vs. 6.6 (±4) |            |                                                                             |                                                                                             |
|                         |      |             | 15 PD–ICD (matched for age, sex, and educational level) |                                      | Mean duration (years): 5.3 (±3) vs. 6.6 (±4) |            |                                                                             |                                                                                             |
|                         |      |             | 24 age- and sex-matched HCs                       |                                        | Mean duration (years): 5.3 (±3) vs. 6.6 (±4) |            |                                                                             |                                                                                             |
| Studies                | Year | Sample size | Participants                        | Disease (type, duration, age at onset) | DA drug (molecule, dosage, duration) | Design                  | Objectives                                                                 | Main results                                                                 |
|-----------------------|------|-------------|--------------------------------------|----------------------------------------|---------------------------------------|--------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Zainal Abidin et al.  | 2015 | 91          | 91 PD patients: 52 with ICB, 39 without ICB | PD                                     | L-Dopa, DDAs                           | 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.          | 2015 | 50          | 32 PD patients: 11 PD + ICD, 21 PD–ICD, 18 age-, sex-, and education-matched HCs | PD                                     | L-Dopa, DAAs (pramipexole, ropinirole, pergolide, amantadine, MAO inhibitors) | Cross-sectional Case-control PET study | To investigate the association between ICD in PD and D₃ receptor availability | D₃ receptor levels were not elevated in PD with ICD |
| Sáez-Francàs et al.   | 2016 | 115         | 115 PD patients: 27 PD with ICD, 88 PD without ICD | PD                                     | DAA, L-dopa, MAO-B inhibitors, amantadine PD + ICD vs. PD–ICD: DAA–EDD = 216 (±135) mg vs. 114 (±135) mg LEDD = 660 (±403) mg vs. 440 (±521) mg | Cross-sectional | To determine the correlates of ICDs                                       | Higher trait anxiety score, Higher impulsivity scores                        |
| Vela et al.           | 2016 | 87          | 87 EOPD patients, age- and gender-matched HCs | PD                                     | 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.          | 2016 | 84          | 84 PD patients: 21 PD + ICD, 63 PD–ICD | PD                                     | 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 |
| 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: 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 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 |
| 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                                     | 1-Dopa (81%) DAAs (pramipexole or ropinirole) (58%) | Cross-sectional Case-control | To determine the correlates of ICDs DRD3 p.Ser9Gly (rs6280) heterozygous variant CT |
| 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 | 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): 6.6 | 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         | PD patients: 70 with ICD; 185 No-ICD | PD | DAAs (pramipexole, ropinirole, bromocriptine, piribedil, rotigotine) | Cross-sectional | To determine the correlates of ICDs | Younger age, Stimulants use | Rapid eye movement sleep disorder behavior |

Table 3 continued

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, DD5 dopamine dysregulation syndrome, DRT dopamine replacement therapy, EOPD early-onset Parkinson’s disease, HC healthy control, ICb impulsive and compulsive behavior, ICB 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.
| Studies            | Year | Sample size | Participants                                      | Disease (duration, type) | DA drug (molecule, dosage, duration) | Design     | Objectives                                      | Main results                                                                 |
|--------------------|------|-------------|--------------------------------------------------|--------------------------|--------------------------------------|------------|-----------------------------------------------|------------------------------------------------------------------------------|
| Pontone et al.     | 2006 | 100         | PD patients (PD + ICD: 9 patients)               | PD                       | Pramipexole, ropinirole, amantadine, entacapone, selegiline, l-dopa | 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.) |
|                    |      |             | PD + ICD vs. PD–ICD:                             |                          | PD + ICD vs. PD–ICD: l-dopa dose = 627 (±281) vs. 520 (±450) mg |            |                                               |                                                                               |
|                    |      |             | Mean age at onset: 44.3 (±9) vs. 48.6 (±9) years |                          | PD + ICD vs. PD–ICD: Mean duration: 4.6 (±62.2) vs. 6.2 (±5.5) years |            |                                               |                                                                               |
| Giladi et al.      | 2007 | 383         | PD patients (PD + ICD: 27 patients; PD–ICD: 166 patients) | PD                       | Ropinirole, pergolide, cabergoline, apomorphine, amantadine, selegiline, entacapone | Cross-sectional | To determine the correlates of ICDs | Younger age at PD motor symptoms onset                                          |
|                    |      |             | PD + ICD vs. PD–ICD:                             |                          | 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   |                          | PD + ICD vs. PD–ICD: Mean duration: 10.3 (±4.9) vs. 9.7 (±6.6) years |            |                                               |                                                                               |
| Kenangil et al.    | 2010 | 554         | PD patients (PD + ICD: 33 patients; PD–ICD: 65 patients) | PD                       | Pergolide, cabergoline, pramipexole, ropinirole, piribedil, lisuride | Cross-sectional | To determine the correlates of ICDs | No significant association with severity of PD or presence of l-dopa-induced motor complications |
|                    |      |             | PD + ICD vs. PD–ICD:                             |                          | PD + ICD vs. PD–ICD: DAA-LEDD = 369 (±181) vs. 319 (±208) mg |            |                                               |                                                                               |
|                    |      |             | Mean age at onset: 49 (±9) vs. 52 (±11) years    |                          | PD + ICD vs. PD–ICD: Total LEDD = 702 (±2369) vs. 640 (±357) mg |            |                                               |                                                                               |
|                    |      |             | Mean duration: 8 (±5) vs. 7 (±5)                  |                          | PD + ICD vs. PD–ICD: Mean duration of DRT: 5.0 (± 3.8) years |            |                                               |                                                                               |
| Lee et al. [102]   | 2010 | 1167        | PG patients                                      | PD                       | 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 |
| 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                       | Bromocriptine, ropinirole, pramipexole, rotigotine, L-dopa | Cross-sectional | To determine the correlates of ICDs          | Younger age at PD onset              |
|                         |      |             |                                                                               |                          | PD + ICD vs. PD–ICD: Mean age at onset: 45.7 (±5.6) vs. 59 (±10.8) years |              |                                                 |                                     |
|                         |      |             |                                                                               |                          | PD + ICD vs. PD–ICD: Mean duration: 13.5 (±5.6) vs. 8.9 (±4.8) years |              |                                                 |                                     |
| Voon et al. [122]       | 2011 | 564         | PD patients: 282 with ICDs 282 No-ICD (matching on age, gender, and DAA treatment) | PD                       | DAAs ± L-dopa                         | Cross-sectional | 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         | PD patients                                                                   | PD                       | Piribedil, pramipexole, ropinirole, bromocriptine, amantadine | Cross-sectional | To determine the correlates of ICDs          | Longer PD duration                  |
| 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                       | L-Dopa, DAAs                          | 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%) |
|                 |      |             |                                                                               | PD + MC vs. PD–MC: Mean age at onset (years): 62 (±10) vs. 63 (±10)            | PD + MC vs. PD–MC: DAA-Ledd (mg) = 73 (±106) vs. 64 (±79) Total Ledd (mg) = 606 (±324) vs. 411 (±238) |               |                                                                            |                                                                                 |
|                 |      |             |                                                                               | Mean duration (years): 11 (±6) vs. 6 (±6)                                    | DAA-Ledd = 168 (±114) mg DAA use: 40/41 vs. 38/48 |               |                                                                            |                                                                                 |
| 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) | Cross-sectional | To determine the correlates of ICDs | Univariate analysis: Younger age at PD onset                                        |
| 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: 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 | To determine the correlates of ICDs and apathy | Univariate analysis: PD + ICD vs. PD + apathy Younger age at PD onset Greater motor disease complexity. |
| 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                       | L-Dopa, DAAs, MAO-B inhibitors       | Cross-sectional with a within- and between-subjects design | To investigate the underlying neurobiology | Relation between aberrant reward processing and DA depletion in the striatum, but not long-term DA medication use |
|                                |      |             |                                                                               |                          |                                      | SPECT coupled with rewarded task-switching paradigm |                                                     | 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                       | DAAs                                 | 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.     | 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.                 | 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.              | 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.               | 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: 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 |
| Studies                  | Year | Sample size | Participants          | Disease (duration, type) | DA drug (molecule, dosage, duration) | Design      | Objectives                              | Main results                                      |
|-------------------------|------|-------------|------------------------|--------------------------|--------------------------------------|-------------|-----------------------------------------|--------------------------------------------------|
| Sáez-Franca`s et al. [94] | 2016 | 115         | 27 PD with ICD 88 PD without ICD | PD                       | DAA, l-dopa, MAO-B inhibitors, amantadine 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-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         | 70 with ICDs 100 No-ICD 285 HCs | PD                       | l-Dopa (81%) DAs (pramipexole or ropinirole) (58%) | Cross-sectional | To determine the correlates of ICDs | Age at PD onset <50 years |
| Ramirez Gómez et al. [96] | 2017 | 255         | 70 with ICD 185 No-ICD | PD                       | DAAs (pramipexole, ropinirole, bromocriptine, piribedil, rotigotine) | Cross-sectional | To determine the correlates of ICDs | Negative association: Presence of dyskinesias and motor fluctuations |

**Table 4 continued**

| 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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