



Impulse control disorders associated with dopaminergic drugs: A disproportionality analysis using vigibase

Laura E. De Wit^{a,e,*}, Ingeborg Wilting^b, Patrick C. Souverein^c,
Peggy van der Pol^d, Toine C.G. Egberts^{b,c}

^aDept. of Psychiatry, University Medical Center Utrecht, the Netherlands

^bDept. of Clinical Pharmacy, University Medical Center Utrecht, the Netherlands

^cDivision of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands

^dTopicus Healthcare, Wageningen, the Netherlands

^eDept. of Psychiatry, Sint Antonius Hospital, Utrecht, the Netherlands

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Abstract

Background: Dopamine receptor agonist drugs, which are used, for example, to treat Parkinson's disease (PD), increase the risk for impulse control disorders (ICDs), potentially resulting in devastating psychosocial consequences. It is unknown whether other drugs with dopaminergic properties also increase the risk for ICDs. This study assesses the disproportionality of reporting ICDs between drugs with dopaminergic properties and selected non-dopaminergic drugs.

Methods: A case/non-case disproportionality analysis was performed, using data from VigiBase (1968–2020). Reports on ICDs as suspected adverse drug reactions (ADRs) were cases ($n=852$), and those with ADRs other than ICDs were non-cases ($n=281,720$). Relative reporting frequencies were expressed as adjusted reporting odds ratios (aRORs). Within the dopamine receptor agonists, the relationship between reporting odds ratios and dopamine receptor occupancy was explored.

Results: A high disproportionality was found for reporting ICDs for all dopaminergic drugs (aROR 20.4 [95% CI 17.4–24.1]) compared to non-dopaminergic drugs. In pharmacotherapeutic subgroups, a high disproportionality was found for primary dopaminergic agents used in PD (aROR 52.1 [95% CI 44.1–61.5]), and to a lesser extent for ADHD psychostimulants and

* Corresponding author.

E-mail address: L.E.deWit-2@umcutrecht.nl (L.E. De Wit).

antidepressants (aROR 5.8 [95% 4.1–8.3] and aROR 3.9 [95% CI 2.9–5.6], respectively). There was no difference in reporting by consumers and healthcare professionals. The highest disproportionality was found for the dopamine receptor agonists pramipexole and ropinirole.

Conclusions: A signal of disproportion in ICD occurrence was found among all investigated drugs with dopaminergic properties, highlighting the importance of counselling and monitoring for ICDs when prescribing dopaminergic drugs.

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1. Introduction

Long-term treatment with dopaminergic drugs in the management of patients with Parkinson's disease (PD) is frequently (13%–24%) complicated by the development of impulse control disorders (ICDs; (Voon et al., 2017; Weintraub et al., 2010; Weiss and Marsh, 2012)). ICDs are a heterogeneous group of disorders, whose core characteristics include repetitive or compulsive behaviour, decreased control over this behaviour, and the pleasant feeling that the behaviour causes (Zhang et al., 2021). ICDs typically involve behaviours such as pathological gambling, hypersexuality, binge eating, and compulsive shopping (Lanteri et al., 2018; Voon et al., 2017, 2009; Voon and Fox, 2007). In addition, behaviours clinically related to ICDs, including punting, dopamine dysregulation syndrome, hoarding, and compulsive medication use, are also recognised (Voon et al., 2017; Zhang et al., 2021). ICDs can have devastating psychosocial consequences for the patient, family, or others (Grall-Bronnec et al., 2018).

Although ICDs can also occur in untreated PD (Antonini et al., 2011; Latella et al., 2019), the initiation of drugs increasing dopaminergic transmission is a precipitating factor (Athanasoulia-Kaspar et al., 2018; Gendreau and Potenza, 2014; Perez-Lloret et al., 2010; Voon et al., 2017). Dopaminergic mesolimbic projections, as well as frontostriatal circuitry, play a major role in the mechanisms of reward and response inhibition, and almost all drugs used in the treatment of PD (except for antimuscarinic drugs) increase dopaminergic transmission in these pathways (Cornelius et al., 2010; Latella et al., 2019; Voon et al., 2017; Zhang et al., 2021). In the largest multicentre study ($n = 3,090$) of ICDs in patients with PD, both dopamine agonist and levodopa use were independently associated with ICDs (Weintraub et al., 2010). This group of disorders also occurs in patients with restless leg syndrome and hyperprolactinemia, treated with dopamine receptor agonists (Bancos et al., 2014; Cornelius et al., 2010; Dang et al., 2011; Martinkova et al., 2011). The development of ICDs has multifactorial causes (Voon et al., 2017) but can be attributed, at least in part, to dopaminergic drugs.

Numerous conditions, including depression and ADHD, are regularly treated with drugs increasing transmission in dopaminergic pathways. Although the increased prevalence of ICDs in PD has garnered much attention (Corvol et al., 2018; Grall-Bronnec et al., 2018; Voon et al., 2017; Weintraub et al., 2010), strikingly little is known about the occurrence of ICDs in the treatment of other disorders with

drugs that have dopaminergic properties. To our knowledge, to date, no studies have evaluated the potential risk for ICDs as adverse drug reactions (ADRs) for the group of drugs with dopaminergic properties as a whole. In this study, we compare the ADR reporting of ICDs in users of dopaminergic drugs to users of selected non-dopaminergic drugs by determining differences in reporting frequency. In addition, we compare reporting frequency between healthcare professionals and consumers. Furthermore, we explore the potential receptor mechanisms of dopamine receptor agonists involved.

2. Experimental procedures

2.1. Setting and study population

Data were derived from VigiBase, the World Health Organization global database of individual case safety reports (ICSRs). VigiBase includes over 20 million reports of suspected adverse effects of drugs, submitted since 1968 (Lindquist, 2008). Over 150 member countries currently register ICSR from sources including physicians, other healthcare professionals, patients, and pharmaceutical companies. Apart from reporting region and source, these pharmacovigilance data include patient demographic characteristics and reported adverse reactions classified according to Medical Dictionary for Regulatory Activities (MedDRA) terms. The completeness of the ICSR is variable, and suspected drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification.

All ICSR in VigiBase related to dopaminergic drugs or selected widely prescribed drugs without dopaminergic effects (see Section 2.2) between 1968 and September 2020 were included. Reports with missing age, sex, reporting year, reporting country, or drug name were excluded. Records sharing the same report ID, substance name, and MedDRA low-level term (i.e., duplicate drug-ADR pairs within each unique ICSR) were merged into one record. Since the ICSR originate from a variety of sources, the likelihood that the suspected adverse reaction is drug-related is not the same in all cases.

2.2. Study design and outcome

Disproportionality analysis, which is a validated case-non-case method in drug safety research, was used to assess

whether ICDs were more frequently reported with dopaminergic drugs compared with selected non-dopaminergic drugs (controls) than would be expected by chance alone (Egberts et al., 2002). Cases were defined using an extended and disproportionality-tested MedDRA list of 24 preferred terms relating ICD (Fusaroli et al., 2021). Preferred terms used (Appendix A) had at least 10 mentions in the reviewed literature. All other events were defined as non-cases (controls).

Furthermore, exposure was defined as the identification of any dopaminergic drug being marked as the suspected drug in an ICSR. 'Dopaminergic drugs' were defined as drugs with full agonistic affinity for dopamine D₁₋₅ receptors, or indirect agonistic activity by inhibition of dopamine reuptake transporter (DAT) or stimulation of release of dopamine via DAT, and/or inhibition of the monoamine oxidase enzyme (MAO).

In order to mitigate competition bias and confounding by indication, non-exposure was defined as the presence of widely prescribed drugs used in a comparable population, but without dopaminergic effects in an ICSR: statins, anticholinergic agents, proton pump inhibitors, bisphosphonates, escitalopram, and citalopram.

For further analysis, dopaminergic drugs were categorised into four pharmacotherapeutic subgroups based on indication: 1. dopaminergic drugs predominantly used in the treatment of PD, consisting of dopamine receptor agonists, a dopamine precursor (levodopa), and enzyme inhibitors (MAO-a and Catechol-O-methyltransferase); 2. ADHD psychostimulants, increasing dopamine signalling by inhibition of reuptake of dopamine and/or stimulation of dopamine release; 3. dopaminergic antidepressants, consisting of dopamine reuptake inhibitors or irreversible enzyme inhibitors (MAO-a and MAO-b); and 4. other: linezolid, an antibiotic with weak, non-selective enzyme-inhibiting (MAO-a and MAO-b) properties.

A list of the included dopaminergic drugs is provided in appendix. Antipsychotic drugs were excluded, since all antipsychotics inhibit dopamine signalling. Furthermore, only FDA- or EMA-approved drugs were included, and a dopaminergic drug had to have at least 100 unique reports for any ADRs to be included in the analysis (list of excluded drugs in appendix).

2.3. Data analysis

First, the distribution of the exposure was compared among cases and non-cases and expressed in a quantitative relative estimate of disproportionality, the ADR reporting odds ratios (RORs), and accompanied by 95% confidence intervals (CIs). The ROR is defined as the ratio of the exposure odds among reported cases to the exposure odds among the non-cases, and it provides an estimate for the risk of developing a certain ADR for patients using the exposure drugs relative to patients using the non-exposure drugs. A signal was considered statistically significant when the lower limit of the 95% CI for the ROR was greater than one. (European Medicines Agency, 2017; Pariente et al., 2012)

Second, the RORs of dopaminergic drugs categorised by their pharmacotherapeutic subgroups were also calculated. Logistic regression analysis was used to calculate the

strength of disproportionality. In our analyses, we adjusted for a number of covariates, namely, age, sex, reporting year, reporting region, and reporter type, and time periods were categorised into four groups: 1968-2004, 2005-2009, 2010-2014, and 2015-2020. Data between 1968 and 2004 were collapsed into one category to create similar-sized groups. Using a stratified analysis by reporter types, adjusted reporting odds ratios (aRORs) for healthcare professionals and consumers were compared.

To explore the association between the mechanism of action of dopamine receptor agonist drugs and ICDs, we compared the receptor occupancy for the dopamine receptors (D₁, D₂, D₃, D₄, D₅) of the dopamine agonist drugs with the corresponding disproportionality signals. In this analysis, ICSRs with more than one suspected dopaminergic drug were excluded.

Occupancy (%) was estimated using the equation $100 \cdot (CU / (K_i + CU))$, where CU (nM) is the unbound drug concentration in blood, and K_i (nM) is the inhibitory constant for each drug (Kenakin, 2004). The CU was calculated using the equation $CU = 1,000 \cdot FU \cdot CT / MW$, where FU is the unbound drug fraction, CT (ng/ml) is the drug concentration in blood, and MW is the molecular weight. To estimate the total drug concentration in blood CT, we used the upper limit of the therapeutic reference range of each dopamine receptor agonist reported (Baldwin and Keating, 2007; Cepaityte et al., 2020; Deleu et al., 2002).

K_i data were obtained from the Psychoactive Drug Screening Program funded by the National Institute of Mental Health (Roth et al., 2000), and when not available, from the International Union of Basic and Clinical Pharmacology (IUPHAR) database (Armstrong et al., 2020). When more than one K_i value was available for a receptor, an average value was calculated. The MW of dopamine receptor agonists was extracted from the IUPHAR database, and the unbound fraction from Drugbank (Armstrong et al., 2020). All data were analysed using SPSS for Windows, version 24.0 (IBM Corporation, Armonk, NY, USA)

3. Results

3.1. Demographics

A total of 282,572 ICSRs was included, consisting of 852 ICSRs related to ICDs (534 male [62.7%]) and 281,720 non-case reports. 'Hypersexuality' was the most frequent ICD reported (155 [17.7%]), with a dopaminergic drug used in PD being the suspected drug in 153 of these reports. The second most reported term was 'impulse control disorder', followed by 'dopamine dysregulation syndrome', and 'gambling'. Feeding and eating disorders (binge eating, food craving and hyperphagia) accounted for 64 (7.6%) of reported ICDs (Table 1). In the subgroup of ADHD psychostimulants, 'impulsive behaviour' and 'hyperphagia' were the most frequent terms reported (both 11 [together 55.0% of total]). In the subgroup of dopaminergic antidepressants, 'hypomania' was the most frequent term reported (27 [43.5% of total]) followed by 'impulsive behaviour' (9 [14.5% of total]). For dopaminergic drugs used in PD, 'impulsive behaviour' was less frequently reported (32 [4.2%]).

Table 1 Frequency of Medical Dictionary for Regulatory Activities (MedDRA) terms identifying impulse control disorder events in reports with suspected dopaminergic drugs.^a

MedDRA List (Preferred Terms)	Total (%)	Healthcare provider N (%)	Consumer N (%)	Other/ unknown N (%)
	N = 874	N = 550	N = 157	N = 167
Hypersexuality	155 (17.7)	116 (21.9)	20 (12.7)	19 (11.4)
Impulse control disorder	152 (17.4)	111 (20.2)	10 (6.4)	31 (18.6)
Dopamine dysregulation syndrome	92 (10.5)	54 (9.8)	23 (14.6)	15 (9.0)
Gambling	81 (9.3)	50 (9.1)	16 (10.2)	15 (9.0)
Compulsive shopping	75 (8.6)	40 (7.3)	19 (12.1)	16 (9.6)
Impulsive behaviour	52 (6.0)	26 (5.4)	14 (10.6)	12 (9.8)
Libido increased	52 (6.0)	24 (4.4)	12 (7.6)	16 (9.6)
Hypomania	52 (6.0)	29 (5.6)	14 (8.9)	9 (5.4)
Gambling disorder (pathological gambling)	37 (4.3)	27 (4.9)	8 (5.1)	2 (1.2)
Stereotypy	29 (3.3)	20 (3.6)	4 (2.6)	5 (3.0)
Hyperphagia	27 (3.1)	8 (1.5)	2 (1.3)	17 (10.2)
Binge eating	23 (2.6)	15 (2.7)	4 (2.6)	4 (2.4)
Food craving	14 (1.6)	8 (1.5)	3 (1.9)	3 (1.8)
Compulsive sexual behaviour	11 (1.3)	5 (0.9)	4 (2.6)	2 (1.2)
Compulsive hoarding	6 (0.7)	5 (0.9)	1 (0.6)	0
Sexual inappropriate behaviour	5 (0.6)	5 (0.9)	0	0
Behaviour disorder	5 (0.6)	3 (0.6)	2 (1.3)	0
Excessive masturbation	4 (0.5)	3 (0.6)	0	1 (0.6)
Excessive sexual fantasies	2 (0.2)	1 (0.2)	1 (0.6)	0
Obsessive need for symmetry, Automatism,	0	0	0	0
Behavioural addiction, Gaming disorder,				
Kluver-Bucy syndrome				

^a An individual case safety report (ICSR) could contain more than one reported adverse drug reaction (ADR); that is, a case could contain more than one item. The total number of MedDRA Terms shown in this table (N=874) therefore does not match the number of cases (N=852).

Almost all ICD ICSRs originated in the Americas (461 [54.1%]) and Europe (352 [41.3%]). The frequency of ICD adverse event reports was highest in 2015 to 2020, accounting for 53.6% (457) of the cases. Most cases were reported for patients aged 45 to 64 years (393 [46.1%]). When stratified by reporter type, ICDs were reported by consumers as often as they were by healthcare professionals (aROR 19.8 [95% CI 16.0–24.8] and aROR 20.5 [95% CI 14.3–29.4], respectively). Additional demographic information can be found in [Table 2](#).

3.2. Impulse control disorder signals and dopaminergic drugs

We found a statistically significant disproportionality signal for reporting ICDs in users of all dopaminergic drugs (aROR 20.4 [95% CI 17.4–24.1]; [Table 3](#)). The second analysis, comparing dopaminergic drugs categorised by their pharmacotherapeutic subgroup to non-dopaminergic controls, revealed that this disproportionality signal was mainly driven by dopaminergic drugs used in PD (aROR 52.1 [95% CI 44.1–61.5]). However, ADHD psychostimulants and dopaminergic antidepressants were also significantly associated with reporting ICDs. ICDs were reported almost six times more frequently in users of ADHD psychostimulants (aROR 5.8 [95% CI 4.1–8.3]) and almost four times more frequently in users of dopaminergic antidepressants (aROR 3.9 [95% CI 2.9–5.6]; [Table 3](#)). In the subgroup of ADHD psychostimulants, the disproportionality signal was mainly driven by

methylphenidate (ROR 3.8 [95% CI 2.4–5.9]). For dopaminergic antidepressants, the signal was mainly driven by bupropion (ROR 1.8 [95% CI 1.3–2.4]) and tranylcypromine (ROR 4.3 [95% CI 1.1–17.5]).

3.3. Relationship between disproportionality for reporting impulse control disorders and dopaminergic receptor occupancy

Occupancy for dopamine receptors (D₁, D₂, D₃, D₄, D₅) was calculated for all dopamine receptor agonist drugs (apomorphine, bromocriptine, cabergoline, pergolide, pramipexole, and ropinirole). [Table 4](#) presents the results for each of these drugs. The ROR for each of the six drugs, analysed individually, was high and statistically significant, except for bromocriptine. A high disproportionality signal was found for agents with a high receptor occupancy of the dopamine D₃ receptor – pramipexole (ROR 49.9 [95% CI 42.1–59.3], D₃ occupancy 85.5%), ropinirole (ROR 36.8 [95% CI 30.3–44.6], D₃ occupancy 27.1), and rotigotine (ROR 8.3 [95% CI 5.3–13.3], D₃ occupancy 23.2).

4. Discussion

Our findings indicate that all drugs with dopaminergic properties are disproportionately more frequently reported as suspected drugs in ICSRs of ICDs. In addition to dopamine

Table 2 Characteristics of reported suspected drug-Adverse-Drug-Reaction (ADR) pairs.

Characteristics	Total ICDs	
	Cases (n = 852)	Non-cases (n = 281,720)
Sex, n (%)		
Female	318 (37.3)	166,594 (59.1)
Male	534 (62.7)	115,126 (40.9)
Age, n (%)		
18-44 years	219 (25.7)	55,582 (19.7)
45-64 years	393 (46.1)	116,953 (41.5)
65-75 years	178 (20.9)	62,478 (22.2)
Aged 75 or older	62 (7.3)	46,707 (16.6)
Region, n (%)		
Africa	0	1,097 (0.4)
Eastern Mediterranean	1 (0.1)	1,418 (0.5)
Europe	352 (41.3)	72,404 (25.7)
Americas	461 (54.1)	104,608 (37.1)
Asia	10 (1.2)	13,295 (4.7)
Western Pacific	28 (3.3)	88,898 (31.6)
Reporter type, n (%)		
Healthcare professional	511 (60.0)	144,539 (51.3)
Consumer	169 (19.8)	43,943 (15.6)
Other or unknown	172 (20.2)	93,238 (33.1)
Reporting year, n (%)		
1968-2004	25 (2.9)	18,744 (6.7)
2005-2009	76 (8.9)	20,466 (7.3)
2010-2014	294 (34.5)	77,124 (27.4)
2015-2020	457 (53.6)	165,386 (58.7)

Table 3 Association between reports of Impulse Control Disorders (ICDs) and exposure to dopaminergic drugs.

	Case (n = 852)	Non-case (n = 281,720)	Crude ROR (95% CI)	Adjusted ROR† (95% CI)
Non-dopaminergic drugs (control)	190	242,187	reference	reference
Dopaminergic drugs (exposure)	662	39,533	21.3 (18.2-25.1)	20.4 (17.4-24.1)
Dopaminergic drugs used in treatment of Parkinson's disease (PD)	566	13,693	52.7 (44.7-62.2)	52.1 (44.1-61.5)
ADHD psychostimulants	40	4,855	10.5 (7.5-14.8)	5.8 (4.1-8.3)
Dopaminergic antidepressants	56	14,162	5.0 (3.7-6.8)	3.9 (2.9-5.6)
Other (linezolid)	0	6,823	NE	

Abbreviations: ROR = reporting odds ratio; CI = confidence interval. †Adjusted for age, sex, region, reporter type, and reporting year.

Dopaminergic drugs used in treatment of PD: Amantadine, Apomorphine, Bromocriptine, Cabergoline, Entacapone, Tolcapone, Levodopa, Pramipexole, Rasagiline, Ropinirole, Rotigotine, and Selegiline

ADHD psychostimulants: Amphetamine, Armodafinil, Dexamfetamine, Lisdexamfetamine, Mazindol, Metamfetamine, Methylphenidate, Modafinil, and Atomoxetine

Dopaminergic antidepressants: Vilazodone, Bupropion, Clomipramine, Desvenlafaxine, Phenelzine, Tranylcypromine, and Moclobemide

receptor agonist drugs, ADHD psychostimulants, in particular methylphenidate, and dopaminergic antidepressants (bupropion and tranylcypromine) are also associated with reporting ICDs. ICDs were reported almost six times more frequently in users of ADHD psychostimulants and almost four times more frequently in users of dopaminergic antidepressants, compared to users of non-dopaminergic agents, thus strengthening the hypothesis that an increase in

dopaminergic activity caused by these drugs might contribute to the development of ICDs.

As expected, we found a high disproportionality for the group of dopaminergic drugs used in PD compared to the group of ADHD psychostimulants and dopaminergic antidepressants. Since ICDs are a known side effect of dopamine receptor agonists and levodopa, clinicians will actively inform patients, and both parties, along with family members,

Table 4 Dopamine receptor agonists associated with Impulse Control Disorders (ICDs).

Dopamine agonist	Number of cases ^a	Number of non-cases	Receptor occupancy profile (%) ^{b, c}					ROR (95% CI) ^d
			D1	D2	D3	D4	D5	
Pramipexole	161	2,103	—	5.4	85.5	—	—	49.9 (42.1–59.3)
Ropinirole	130	1,767	—	63.5	27.1	—	—	36.8 (30.3–44.6)
Cabergoline	15	664	46.8	—	—	—	89.4	10.5 (6.4–17.0)
Rotigotine	16	927	0.1	95.1	23.2	2.3	1.2	8.3 (5.3–13.3)
Apomorphine	7	680	0.04	—	—	—	—	5.6 (2.7–11.9)
Bromocriptine	3	1,066	—	9.7	5.7	—	0.1	1.1 (0.3–3.5)

Abbreviations: ROR = reporting odds ratio; CI = confidence interval.

^a Cases with multiple suspected dopaminergic drugs were excluded from this analysis.

^b Estimated using $100 \cdot (\text{CU} / (\text{K}_i + \text{CU}))$. CU (nM) = unbound drug concentration in blood. K_i (nM) = inhibitory constant.

^c Only full agonist activity is shown.

^d The group of non-dopaminergic drugs was used as reference.

will vigilantly monitor the development of ICDs in patients using these drugs. This aspect, as well as notoriety bias, may have contributed to the high rate of this reported side effect (Grosset et al., 2006; Moore et al., 2014; Voon et al., 2017).

The specific action of dopamine receptor agonists on the dopamine D₃ receptor is suggested to play an important role in the development of ICDs, as an association was observed between ICDs and dopamine agonists with higher dopamine D₃ receptor affinity (Garcia-Ruiz, 2019; Seeman, 2015; Voon et al., 2017). Nevertheless, in a prospective report of 297 patients with PD screened on pathological gambling, no association with an agonist subtype was observed (Voon et al., 2006). In this study, we found a high disproportionality for the dopamine receptor agonists pramipexole and ropinirole. This could reflect high occupancy of the dopamine D₃ receptor; however, pramipexole and ropinirole are not exceptional in their dopaminergic properties (Lader, 2008), and we found no clear relationship to the relative reporting frequencies and the degree of receptor occupancy.

We also found no difference in the reporting of ICDs by patients and healthcare professionals. This is in contrast with previous studies showing that patients are more likely to report ADRs regarding psychiatric symptoms (RR 1.48) and ADRs influencing social circumstances (RR 2.07; (Banovac et al., 2017)). In general, patients are more inclined to report ADRs that have a direct impact on quality of life. We therefore expected to find a discrepancy in reporting ICDs, with a higher relative reporting frequency for ICDs in patients. Our findings suggest that, compared to other psychiatric ADRs, patients might recognise an ICD as an ADR less often. Furthermore, because of humiliation, patients might not spontaneously disclose uncontrollable urges to engage in sexual activity, gambling, or excessive spending. This is in agreement with other studies showing that even in situations where the treating physician was aware of the relationship between dopaminergic therapies and ICDs, the disorders remained undetected in over 50% of the patients who suffered from one (Weiss et al., 2010; Weiss and Marsh, 2012). The potential for ICDs and related behaviours should therefore be raised as potential side effects before the initiation of dopaminergic drugs, and family members should be involved in the counselling, as some pa-

tients might lack insight into their behaviours (Evans et al., 2009; Grosset et al., 2006).

In some conditions treated with dopaminergic drugs, it is possible that our target event (an ICD) may be confused with a symptom of the underlying condition. Since ADHD is characterised by inattention, limitation of response inhibition (impulsivity), and hyperactivity, some symptoms of ADHD may be difficult to distinguish from ICDs. The development of ICDs during treatment with psychostimulants could therefore mistakenly be identified as a worsening of ADHD and hence as ineffectiveness of the drug, rather than a side effect. This might have led to underreporting (competition bias), along with the fact that ICDs are not yet registered as side effects of ADHD psychostimulants and dopaminergic antidepressants, thereby making an ICD less likely to be recognised as a side effect. (Zeiss et al., 2021) As mentioned above, patients with PD might have a biological predisposition towards ICDs (Voon et al., 2017); however, dopaminergic drugs used in the treatment of this disorder already have boxed warnings about the potential for the development of ICDs and these ICDs are therefore less overlooked, which is also evident from the high relative reporting frequency found in this study.

‘Hypomania’ was the most frequent ICD reported in ICSRs of dopaminergic antidepressants. It is well known that patients may develop hypomania symptoms upon use of antidepressants, especially in case of an underlying bipolar vulnerability. (Barbuti et al., 2017; Gijssman et al., 2004; McIntyre et al., 2020) Nevertheless, in the literature the preferred term ‘hypomania’ has also been extensively associated with ICDs (Fusaroli et al., 2021). This issue highlights that ICDs still have not found a stable and harmonical placement within taxonomies. Going forward, the search will continue for a MedDRA list of conditions relating ICDs that is broad enough to capture small signals, but also narrow enough to maintain specificity.

A strength of our study is the data source that is used. Vigibase is the largest available pharmacovigilance database, with over 20 million ICSRs, thereby allowing us to perform disproportionality analyses with high statistical power. It also enabled us to evaluate unexpected or unknown reported ADRs. Moreover, the disproportionality analysis is a validated method in drug safety research and surveillance (Egberts et al., 2002; Montastruc et al., 2011). When

calculating specific RORs for dopamine receptor agonist drugs, reports with multiple dopaminergic agents as suspected drugs were excluded. This allowed the ROR found to be more purely related to the pharmacological mechanism of action. Additionally, we reviewed available pharmacodynamic sources to map the pharmacodynamic profile of dopamine receptor agonists to relate the risk for reporting ICDs with occupancy on the dopamine receptors.

Our data share the limitations inherent in pharmacovigilance databases, with insufficient data available to investigate indication, severity, dose, or treatment duration. The number of reports does not provide information about incidences, because of differences in exposure and variability in reporting rates (Potlog Shchory et al., 2020). While underreporting is expected, serious ADRs, such as ICDs, are more likely to be reported (Hazell and Shakir, 2006). Given the spontaneous nature of ADR reporting to Vigibase, our findings provide a signal regarding differences in both the occurrence of ICDs and the use of different dopaminergic drugs, but they do not allow for an absolute and relative reporting rate (Greenblatt, 2015).

Although third-generation antipsychotics (aripiprazole, brexpiprazole and cariprazine), have been associated with ICDs (Grall-Bronnec et al., 2016; Zazu et al., 2021), the net mechanism of action (pharmacodynamic effect) is aimed at a reduction of dopaminergic (D_2) neurotransmission (Stahl et al., 2021). Therefore, these agents were excluded in this study. Several dopaminergic drugs analysed in this study may target additional receptors, including serotonergic receptors. The mechanism of development of ICDs is complex and cannot be attributed solely to the pharmacodynamic effects of dopaminergic drugs.

We considered whether our methods might have produced unintentionally biased results. First, comedication (such as GABA agonists, dopamine antagonists, glutamatergic agents, or antiepileptics) was not tested as a potential confounder in the multivariable regression analysis. Such comedication could lead to underreporting, since these drugs could be used to treat ICDs and thus could mask a potential development of those disorders (Garcia-Ruiz, 2019; Schreiber et al., 2011; Voon et al., 2017).

The second unintentionally biased result could stem from the Weber effect, signifying that newer agents receive critical assessments and thus relatively more ADR reports in the first years to market (Stephenson and Hauben, 2007). However, as it is unlikely that this would disproportionately affect cases or non-cases, this effect is unlikely to bias our results. Third, we investigated whether external events might have stimulated an unusual number of reports, but the trend over time for reports of ICDs exhibited a steady growth for over a decade. In the disproportionality analysis, specific drugs used in comparable populations and without dopaminergic properties were selected for comparison (appendix), attempting to limit the risk of competition bias and confounding by indication.

5. Conclusion

Our findings demonstrate that the use of all drugs with dopaminergic properties is associated with the reporting of ICDs. The occurrence of ICDs can cause embarrassment or

social exclusion. Moreover, patients, their families, or clinicians may confuse an ICD with a symptom of the underlying condition and mistakenly identify it as ineffectiveness of the drug, resulting in unnecessary switching of therapy, or they may not even recognise the disorder as a side effect. Therefore, patients using drugs with dopaminergic properties should be carefully monitored and counselled about the risk of development of ICDs.

Author contributors

Authors L.E. De Wit, I. Wilting, P.C. Souverein and A.C.G. Egberts designed the study and wrote the protocol. Author L.E. De Wit managed the literature searches and analyses. Authors L.E. De Wit and P. van der Pol undertook the statistical analysis, and author L.E. De Wit wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Declaration of Competing Interest

drs. L.E. De Wit has nothing to disclose, dr. I. Wilting has nothing to disclose, dr. P.C. Souverein has nothing to disclose, dr. P. van der Pol has nothing to disclose, prof.dr. A.C.G. Egberts has nothing to disclose

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.euroneuro.2022.01.113](https://doi.org/10.1016/j.euroneuro.2022.01.113).

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