Exploring the underlying mechanisms of drug-induced impulse control disorders: a pharmacovigilance-pharmacodynamic study

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Running title: Impulse control disorders' pathogenesis

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Abstract

Introduction: Impulse control disorders (e.g., pathological gambling, hypersexuality) may develop as adverse reactions to drugs. Pathogenetic hypotheses have mainly focused on D3-receptor agonism, and switching to alternatives with different pharmacologic mechanisms represents a common management strategy. Nonetheless, treatment failure is common and gaining pathophysiological insights is needed.

Aim: We aimed to identify targets potentially contributing to pathologic impulsivity.

Method: We performed a pharmacovigilance-pharmacodynamic study on dopamine agonists and antipsychotics using the Food and Drug Administration Adverse Event Reporting System (January 2004-December 2021). We estimated disproportionate reporting using the Bayesian information component. Using online public databases (IUPHAR, ChEMBL, PDSP, DrugBank), we calculated drug occupancies. To identify the targets potentially contributing to impulsivity, we fitted univariate regression models interpolating information components and occupancies within dopamine agonists and antipsychotics. Sensitivity analyses were performed to check for the robustness of the results.

Results: Among 19,887 reports of impulsivity, 5,898 recorded an antipsychotic, and 3,100 a dopamine agonist. The more robust signals concerned aripiprazole (N=3,091; median information component [95% confidence interval] = 4.51[4.45-4.55]) and brexpiprazole (229; 4.00[3.78-4.16]) for antipsychotics, pergolide (105; 5.82[5.50-6.06]) and pramipexole (2009; 5.43[5.36-5.48]) for dopamine agonists. Robust, significant positive associations between drug occupancy and impulsivity reporting were found for D3 within dopamine agonists (beta=1.52; p-value=0.047) and 5-HT1a within antipsychotics (1.92, 0.029).

Conclusion: Our results supported the role of D3-receptor agonism in inducing impulsivity in dopamine receptor agonists and identified a potential role of 5-HT1a receptor agonism in antipsychotics. Investigating these receptors may drive towards a better management of drug-induced impulsivity.

Keywords: Disruptive, Impulse Control, and Conduct Disorders; Dopamine Agonists; Drug-Related Side Effects and Adverse Reactions; Impulsive Behavior; Psychopharmacology

1. Introduction

Impulse control disorders (ICDs) are both idiopathic and drug-induced behavioral addictions[1] (e.g., pathological gambling, hypersexuality, compulsive shopping). Even if they manifest as willing acts aimed at gratification, in the beginning, they commonly turn into compulsions when left untreated[2], with juridical, psychosocial, and economic consequences. For example, due to pathological gambling, patients may steal money to persist in their addiction, lose their work, declare bankruptcy, divorce, and commit suicide. Despite their seriousness, no pharmacological option has still been approved to treat ICDs.

Drug-induced ICDs may develop with dopamine agonists used in Parkinson's disease, prolactinoma, and restless leg syndrome[3], but also with dopamine partial agonists used in schizophrenia and mood disorders[4,5]. Recently, a nationwide registry-based study in Sweden found a significantly higher frequency of gambling disorders in patients using dopamine agonists compared to patients using other dopaminergic drugs (OR [95% CI] = 3.2 [1.4–7.6], p=0.008)[6], and a pharmacovigilance study on the WHO spontaneous reporting system investigated the association between dopaminergic agents and the reporting of ICDs[7]. These drug classes have access to the brain to deliver their therapeutic action and partly overlap in their pharmacodynamic profile, particularly on catecholaminergic pathways, which may therefore be involved in ICDs development.

The ventral striatum and dopamine have a pivotal role in the gratification pathway, physiologically involved in craving fitness-improving behaviors and avoiding fitness-disruptive ones. In the ventral striatum, the tonic release of dopamine results in the binding of D2, a Gi-protein coupled receptor inhibiting the indirect pathway and facilitating daily behaviors[8,9]. When an appetitive stimulus preluding to gratification synchronizes the release of dopamine by presynaptic neurons, resulting in a phasic burst of dopamine, high dose dopamine also binds D1, a Gs-protein coupled receptor activating the direct way and promoting totalizing gratification-driven behaviors[10,11].

Dopamine agonists, administered to compensate for the hypodopaminergic status in the degenerated dorsal striatum and to relieve motor symptoms in Parkinson’s disease, may also cause a hyperdopaminergic status in the healthy ventral striatum and induce the dysfunctional drive characteristic of ICDs[12]. In particular, the D3 receptor, similar to D2 but localized in the ventral striatum, is a preferential target of dopamine agonists[13]. Coherently, it is a common practice, when ICDs develop, to reduce the dose or switch from high to low D3-affinity dopamine agonists. Nonetheless, these strategies have proven a limited efficacy: in a

longitudinal study, only 50% of the patients improved after one year[14]. Furthermore, these hypotheses do not exhaustively explain experimental data. In impulsive rats, the D2 and D3 receptors are reduced[15], and a dopamine receptor antagonist can have opposite effects when injected into different portions of the ventral striatum[16]. In ICD patients with Parkinson's disease, a gratification-preluding stimulus activates the ventral striatum increasing the release of endogenous dopamine[17,18] and D3 receptors are reduced in the ventral striatum[19,20]. The hypothesis that ICDs develop due to the administration of exogenous dopamine agonists is not entirely coherent with these findings, which instead suggested an indirect increase of dopamine release in the ventral striatum.

Given the high failure rate of common practices for ICDs management[14], together with the high risk of losing control over Parkinson's symptoms and the possibility of a withdrawal syndrome[21], physicians might prefer not to switch to alternative therapies despite ICDs life-impacting sequelae.

In fact, many other neurotransmitters and neuroanatomical structures are involved in addictions[22–25] and are targeted by dopamine agonists. Among this richness of molecular targets, there is plausibly the key to better management of drug-related ICDs. Integrating pharmacovigilance and pharmacodynamic data may help in the search for the pathogenetic mechanisms of drug-induced conditions[26–40]. Therefore, we aim to generate novel hypotheses on the underlying mechanistic basis of drug-induced ICDs. A more comprehensive understanding of the role of other molecular targets would drive a more successful drug switching in case of ICDs onset and may support the development and repurposing of pharmacological treatments for ICDs.

2. Methods

2.1 Pharmacovigilance Data

We extracted pharmacovigilance data from the FDA Adverse Event Reporting System (FAERS), a spontaneous reporting system collecting worldwide reports of suspect adverse drug reactions. We downloaded quarterly data from January 2004 to December 2021 (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html), merged and cleaned them accordingly to previous works[41,42].

We selected *a priori* the drugs of interest based on the Anatomic Therapeutic Chemical (ATC) classification, identifying two populations of interest: a) reports recording the use of

dopamine agonists, included in the ATC categories N04BC (dopamine agonists for Parkinson's Disease) and G02CB (prolactin inhibitors); b) reports recording the use of antipsychotics, included in the ATC category N05A. We identified ICD events in the reaction fields by adapting a query from a previous work, including pathological gambling, hypersexuality, paraphilic disorders, compulsive shopping, hyperphagia, pathological gaming, pyromania, kleptomania, hoarding disorder, excessive exercise, overwork, poriomania, body-focused repetitive behaviors, and stereotypy[43] (see Supplementary Material – Table S1). This query is implemented in the Medical Dictionary for Regulatory Activities (MedDRA), used to code both suspect reactions and reasons for use in the FAERS.

We compared ICD and non-ICD reports within antipsychotics and dopamine agonists, separately, to better characterize ICDs. We used the chi-square test for categorical variables and the Kruskal-Wallis test for continuous ones, correcting the p-values for multiple testing with Holm-Bonferroni. We considered statistically significant p-values lower than 0.05 after the correction.

Using a 2*2 contingency table, we calculated the Bayesian Information Component (IC) as a measure of disproportionate reporting of ICDs with a specific drug, against all other reports in the FAERS. A significant disproportion was defined as 95%CI lower bound of the IC higher than 0. IC allows to correct for small numbers of cases[44]. Nonetheless, we set a precautionary threshold of ≥10 cases to perform disproportionality analysis.

2.2 Pharmacodynamic Data

We extracted pharmacodynamic data using multiple databases publicly available online. To globally consider both pharmacokinetic and pharmacodynamic characteristics of the drugs investigated, we chose as main parameter the receptor occupancy: the percentage of binding sites of a molecular target forming a bond with the drug. Calculation of the occupancy was based on the following:

$$f_{occ} = f([C_r]) = \frac{1}{1+\frac{K_i}{[C_r]}} \qquad \text{[formula 1]}$$

$$[C_r] = \frac{1000 \times F_u \times C_{max}}{M_r} \qquad \text{[formula 2]}$$

In order to estimate maximum concentrations in the blood (C_{max}), we used therapeutic ranges from the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology[45]. We then retrieved molecular weights (M_r) from the International Union of basic and clinical PHARmacology (IUPHAR) (https://www.guidetopharmacology.org) and fractions unbound (F_u) from DrugBank[46] to calculate the free-drug serum concentration (C_r, i.e., the concentration available for binding receptors). To calculate the occupancy on each receptor for all the drugs of interest on the basis of free-drug concentrations, we also needed receptor affinity measures (K_i). Because there are inconsistencies between different databases concerning *Homo sapiens* Ki values, we systematically extracted them according to an *a priori* hierarchical search: first in the IUPHAR, in case of missing data in the European Bioinformatics Institute-ChEMBL[47], and only at last in the Psychoactive Drug Screening Program (PDSP, at https://pdsp.unc.edu/databases/kidb.php)[48]. When multiple Ki values were reported in a database, we calculated their geometrical mean. We did not restrict to *a priori* defined receptors.

For a more informative visualization and the implementation of sensitivity analyses, we retrieved drug activities (full agonist, partial agonist, antagonist, inverse agonist, not specified) from DrugBank and, when not available, from IUPHAR.

2.3 Pharmacovigilance-Pharmacodynamic Models

We developed linear regression models for antipsychotics and dopamine agonists, separately, to account for a plausible indication bias (i.e., despite the evidence of ICD occurrence in Parkinson's disease, ICD symptoms are generally related to psychiatric conditions[49]). For each molecular target, we reported the occupancy on the x-axis and the IC on the y-axis. We fitted a univariate linear regression model to each plot if at least 3 specific drug-related occupancies were available. Multivariate models considering multiple receptors were not performed because the different drugs have different targets and missing data would invalidate the model. We considered as plausible mechanisms those receptors with a p-value of the b coefficient lower than 0.05. We did not apply any correction for multiple testing because of the hypothesis-generating nature of our study: missing a true association would have a higher cost than including a spurious one. We plotted the regression line together with the 95% Confidence Interval (CI) and the original points corresponding to the drugs under study (color-coded to show different activities: full agonist, partial agonist, antagonist, inverse agonist).

Because many assumptions must be made in our models, we also implemented 4 sensitivity analyses to assess the robustness of the results, i.e., to check whether the model went in the same direction and was still significant across the analyses.

a) Receptor occupancy is considered the best way to approximate drug-receptor activity. However, given the multiple data required for the calculation, the risk of missing data is high. Therefore, we used pKi values, instead of occupancy, to decrease the proportion of missing data.
b) Drugs may have different actions on the receptor and may therefore be classified, at least, as agonist, antagonist, partial agonist, and inverse agonist agents. Thus, an agonist and an antagonist with the same affinity may have opposite effects. To take this into account, we reversed the sign of receptor occupancy for antagonist and inverse agonist drugs. Drugs for which we were not able to retrieve the activity were excluded from these models.
c) Because linear regression models are very sensitive to outliers, we assessed the robustness of the relationship by excluding outliers from the sensitivity analysis b).
d) Finally, following the hypothesis of shared receptors in the development of drug-induced ICDs, we repeated the sensitivity analysis b) considering antipsychotic and anti-Parkinson's agents together. We estimated a mixed-effects regression model with a random intercept for drug class to account for potential differences between antipsychotic and anti-Parkinson's classes.

The sensitivity analyses a), b), and c) were performed separately by drug class. Each emerging relationship was defined as highly robust if supported (significant and same direction after correcting for activity) by all the sensitivity analyses, as robust if supported by at least two over four sensitivity analyses, and as non-robust if supported by less than two sensitivity analyses.

2.4 Statistical tools

All data-preprocessing, statistical analyses and visual representations were obtained using R version 4.1.2 (2021-11-01).

3. Results

3.1 Pharmacovigilance Data

First, we needed to obtain the measures of disproportionate reporting. We cleaned the FAERS and retrieved 19,887 ICD reports (0.17%), with pathological gambling and hypersexuality being the most reported ICD conditions in both antipsychotics and dopamine agonists (see Figure S1). Antipsychotics were reported in 5,898 (29.66%) ICD reports, with the three MedDRA preferred terms most reported as reasons for use being bipolar disorder (1324, 30.98%), major depression (1133, 26.51%), and schizophrenia (939, 21.97%). Dopamine agonists were reported in 3,100 (15.59%) ICD reports, with the main reasons for use being Parkinson's disorder (1550, 59.75%), restless leg syndrome (880, 33.92%), and prolactin-producing pituitary tumor (49, 1.89%). Other drugs reported as primary suspects in ICD reports were antidepressants (1942, 9.77%), antiepileptics (1325, 6.66%), and psychostimulants (1213, 6.10%).

Within the two populations (i.e., dopamine agonist reports and antipsychotic reports, see Supplementary Material – Table S2-S3), ICD reports were characterized by a significantly higher proportion of men (50.58% vs 47.56% in antipsychotics; 59.90% vs 39.46% in dopamine agonists) and younger age (median[Q1-Q3] = 42 [29-55] years vs 50 [34-64] in antipsychotics; 56 [48-65] vs 66 [55-75] in dopamine agonists). Lower proportions of deaths (2.05% vs 12.20% in antipsychotics; 2.42% vs 7.62% in dopamine agonists) and higher of disability (9.60% vs 1.95%; 4.42% vs 2.26%) were also reported. The onset of ICDs was earlier for antipsychotics (median[Q1-Q3] = 31 [1-366] days, on 1,871 available time to onset data) than for dopamine agonists (214 [24-731] days, on 662 available time to onset data). Dopamine-agonist related ICDs, compared to antipsychotic-related ICDs, also had higher contribution by men (59.90% vs 50.58%) and older people (56 [48-65] vs 42 [29-55] years old). Finally, the 254 ICD cases recording the use of both dopamine agonists and antipsychotics (Table S4) shared the characteristics of ICDs occurring with dopamine agonists (men 60.00%, age 56 [45-67], but were more similar to ICDs occurring with antipsychotics in the lawyer contribution (15.29%) and the reported disability rate (8.27%), and the reported hospitalization rate (42.13%) was substantially higher than when developing ICDs with dopamine agonists (16.84%) or antipsychotics (32.50%).

Significant and non-significant results of the disproportionality analysis (information component, IC) were reported in Supplementary Material – Table S5-S6 and in Supplementary Material section B. On 66 antipsychotics, 33 with ≥10 cases, we obtained 32 statistical signals,

the strongest (i.e., signals with the highest lower extremity of the 95%CI of the IC) being aripiprazole (N = 3,091; median IC [95%CI] = 4.51[4.45-4.55]), brexpiprazole (N = 229; 4.00[3.78-4.16]), and cariprazine (N = 49; 3.02[2.54-3.36]). On 12 dopamine agonists, 9 with ≥10 cases, we obtained 9 statistical signals, the strongest being pergolide (N = 105; 5.82[5.50-6.06]), pramipexole (N = 2009; 5.43[5.36-5.48]), and piribedil (N = 48; 5.01[4.53-5.36]).

3.2 Pharmacodynamic Data

Using pharmacokinetic public online databases, due to missing therapeutic range data, we obtained free-drug serum concentration for 19/32 antipsychotics and 5/9 dopamine agonists disproportionally reported with ICDs. We then integrated K_i receptor affinity measures to calculate the occupancies. Twenty receptors had at least 3 available antipsychotics-related occupancies (5-hydroxytryptamine receptor 5-HT, types 1a/2a/2b/2c/6/7; dopamine receptor D, types 1/2/3/4/5; histamine receptor H, types 1/2; adrenergic receptor A, type 2c; serotonin transporter SERT; muscarinic receptor M, types 1/2/3/4/5) and 7 receptors had at least 3 available dopamine agonists-related occupancies (5-HT, types 1a/2a; D types 1/2/3/4/5). Single parameters are available in the Supplementary Material – Table S5-S6.

3.3 Pharmacovigilance-Pharmacodynamic Models

To identify the relationship between each drug receptor occupancy and its ICD disproportionate reporting, we performed univariate linear regression models (see Supplementary Material – Table S7) and four sensitivity analyses (see Supplementary Material – Table S8). In the main analysis, we found two significant positive associations between occupancy and reporting of ICDs (median IC): 5-HT1a-receptor agonism showed a highly robust positive association with the reporting of ICDs within antipsychotics ($\beta = 1.924$, $p = 0.029$, $R^2 = 0.307$); D3-receptor agonism showed a robust positive association with the reporting of ICDs within dopamine agonists ($\beta = 1.516$, $p = 0.047$, $R^2 = 0.707$) (see Figure 1). Within antipsychotics, we also observed negative associations with antagonism on three receptors: D1-receptor antagonism ($\beta = -2.511$, $p = 0.014$, $R^2 = 0.603$) and M3-receptor antagonism ($\beta = -2.129$, $p = 0.025$, $R^2 = 0.997$) showed to be robust hypotheses at the sensitivity analyses; M4-receptor antagonism ($\beta = -1.951$, $p = 0.029$, $R^2 = 0.914$) showed to be non-robust.

4. Discussion

4.1 Pathogenetic hypotheses for drug-induced ICDs

Pharmacovigilance-pharmacodynamic studies are a novel pharmacoepidemiologic approach to investigate the molecular mechanisms underlying adverse drug reactions, especially in those therapeutic areas involving active substances that vary greatly in characteristics and targets[33]. For example, they were recently applied to investigate the pathogenesis of antipsychotic-induced hyponatremia[34], pneumonia[27], diabetes[35], Parkinsonism[37]. Our pharmacovigilance-pharmacodynamic analysis is the first study aimed at evaluating the association between ICDs and the pharmacodynamic profile of anti-Parkinson and antipsychotic dopaminergic agents.

From the main analyses, two key findings emerged, including novel mechanistic hypotheses: 1) D3 receptor occupancy and agonism in dopamine agonists, and 5-HT1a receptor occupancy and agonism in antipsychotics were significantly associated with a higher reporting of ICDs; 2) D1, M3, M4 receptor occupancy and antagonism in antipsychotics were significantly associated with a lower reporting of ICDs (see Figure 2). Activity on the 5-HT1a receptor showed the highest robustness, being confirmed in all four disproportionality analyses. The other receptors were supported by at least two disproportionality analyses, apart from M4, which found no further support. Other receptors emerged only from the sensitivity analyses and may therefore constitute less robust hypotheses.

4.2 The potential contribution by D3-receptor agonism

As anticipated, the association between D3-receptor agonism and the development of dopamine agonists-related ICDs has already been established and impacts clinical practice[13], even if per se it cannot fully explain accruing evidence. D3 is a receptor of the D2-subfamily, involved in facilitating movements and behaviors through the inhibition of the indirect pathway, but with a preferential location in the ventral striatum[50]. The association we found between D3-receptor agonism and ICD development or precipitation is, therefore, coherent with accrued evidence and has already been implemented in the clinics.

4.3 The potential protective role of D1-receptor antagonism

For the first time, we put forward a potential protective role of D1-receptor antagonism, which is biologically plausible. The D1 receptor is a widely expressed Gs-protein coupled

receptor, particularly localized in the prefrontal area and ventral striatum[10,51]. Since dopamine activity on D1, activating the direct pathway, physiologically promotes totalizing reward-driven behaviors, D1-receptor antagonism plausibly suppresses craving and protects against ICDs.

Coherently, in patients with Parkinson, Positron Emission Tomography (PET) approaches have indicated decreased D2R binding and relatively unchanged D1R binding in the ventral striatum in those affected by ICD compared with patients without ICDs[52]. Furthermore, Erga et al. identified an increased risk of ICDs in patients with gene polymorphisms in the 5′ untranslated region (UTR) of the DRD1 gene, which encodes the dopamine receptor D1[51]. Other polymorphisms in DRD1 have been linked to ICDs, neuropsychiatric disease, problem gambling, addiction, and cognitive functioning in non-PD populations[53,54].

Even if previously underestimated, the potential involvement of D1 in the precipitation of ICDs and the potential protective role of D1-receptor antagonism are thus biologically plausible and need to be further investigated.

4.4 The potential contribution by 5-HT1a-receptor agonism

The role of 5-HT1a, whose association with ICDs reporting was consistent in all the analyses performed within antipsychotics and in the mixed-effects model, has been neglected so far. Serotonin has an important role in modulating reward-driven behaviors, but the mechanism is still unclear[55]. Among theories so far developed, the core idea ascribes an inhibitory role on ventrotegmental dopamine neurons, avoiding that the pursuit of negligible rewards precludes the acquirement of greater rewards. In particular, they would activate ventrotegmental GABAergic interneurons through 5-HT2c, a Gq-protein coupled receptor[56].

5-HT1a is a G_i-protein coupled autoreceptor localized in the dorsal raphe that, when activated, inhibits the serotonergic projections to the ventrotegmental area. Therefore, it may potentially contribute to the development of ICDs by inhibiting the serotonergic pathway usually involved in impulse control, resulting in an increased motivational drive. Indeed, its agonism, particularly at low doses, was observed to induce-reward-driven behaviors[57]; 5-HT1a-receptor agonism has been found to induce impulsivity in mice[58,59] and rats[60–62]; 5-HT1a-receptor antagonism reduces impulsivity in rats[63]; 5-HT1A gene polymorphisms bring susceptibility in humans[64,65].

Therefore, we believe that our hypothesis including 5-HT1a-receptor agonism as one of the main pathogenetic mechanisms of iatrogenic ICDs is promising and deserves to be further investigated.

4.5 The potential protective role of M3 and M4-receptors antagonism

Finally, also M3 and M4 receptors have been so far neglected when investigating drug-induced ICDs. However, they are important in the aversion-driven blockade of behaviors that oppose reward. Data on aversive stimuli and reward omission (e.g., from the amygdala, lateral habenula, laterodorsal tegmentum, and pedunculopontine nucleus) converge into the rostromedial tegmental nucleus and modulate the activity of GABAergic neurons that inhibit ventral tegmental dopaminergic neurons and behaviors[66]. The laterodorsal and pedunculopontine neurons, in particular, contribute with cholinergic input that, through the post-synaptic muscarinic G_q-protein coupled receptor M3, activates the GABAergic neurons and inhibits behaviors. Acetylcholine also starts negative feedback mediated by the pre-synaptic muscarinic G_i-protein coupled receptor M4, which reduces acetylcholine release, and therefore contrasts the acetylcholine-mediated activation of GABAergic neurons[67]. Therefore, it is biologically plausible that M4 receptor antagonism, impairing this negative feedback, may reduce ventrotegmental neurons activity and protect against ICDs. The protective role of M3-receptor antagonism is instead more difficult to explain since, in theory, it should result in lower GABAergic activity and facilitated behaviors. Nonetheless, the M3 receptor subtype is only one activating rostromedial tegmental GABAergic neurons, and its incapacitation does not directly result in the facilitation of reward-driven behaviors. The ability of M3-receptor antagonism to predict ICDs development may indeed be associated with a shared affinity for M3 and M4 receptors, rather than with an effective protective role of M3-receptor antagonism.

Coherently, even if tropicamide, an M4-receptor antagonist, was observed to induce reward-driven behaviors in mice[67], muscarinic receptor antagonism has shown fewer risk-taking behaviors in rats[68], and mice lacking M4 in cholinergic receptors were unable to learn positive reinforcement[69]. Nonetheless, contrary to the literature, it should be noted that no sensitivity analysis supported the role of M4. It is therefore unclear whether M4-receptor antagonism is a mechanism that should be further investigated in the attempt to understand and manage ICDs.

4.6 Strengths and limitations

Because of the many limitations of pharmacovigilance and the lack of consensus for pharmacovigilance-pharmacodynamic studies, our study design is only intended to generate hypotheses, and the preliminary results we obtained should not directly influence clinical practice. Nonetheless, we implemented multiple sensitivity analyses to assess the robustness of our results when adopting different strategies.

Spontaneous reports are often unverified, duplicated, influenced by reporting biases, and disproportionality measures may go out of scale in the presence of few cases. In particular, spontaneous reporting systems are likely affected by reporting biases, including underreporting. Further, for ICDs, also overreporting is a non-negligible phenomenon: while contributions by patients and their families make spontaneous reporting systems a preferential source of information about stigmatized psychosocial conditions such as ICDs, these reports are usually unverified and may be submitted for personal interests. For example, 22.43% of antipsychotic-related ICD reports were submitted by lawyers and may have been driven by law court reasons rather than by a proper causality assessment. Furthermore, to retrieve cases of interest, we have to rely only on the information provided with the report and a proper assessment following diagnostic criteria cannot be performed. We retrieved the cases based only on the reporting of a behavioral addiction in the event field assuming that an event, to be reported, must have an impact on the life of the patient. For these reasons, disproportionality analyses can only be used to generate hypotheses and cannot provide incidence measures. To partly account for these biases, we pre-processed the FAERS for duplicates removal, used a threshold of 10 cases, and calculated the Bayesian IC, correcting for small numbers[44], as a measure of disproportionate reporting.Pharmacodynamic databases have the problems of missing data, multiple affinity values (i.e., different in the choice of parameters and competitor), and duplicates. We performed a systematic collection of affinity data, gathering affinities from the most reliable database (IUPHAR if possible, otherwise ChEMBL and PDSP), excluding plausible duplicates, and performing the geometrical mean in case of multiple values.

Because of the limited number of drugs investigated and because of missing pharmacodynamic data, we performed univariate linear regression models. However, in the presence of more complete data, other models might be more appropriate to visualize the relationship between receptor-activity and adverse drug reactions.

Other aspects must be kept in mind. The nature of this study is hypotheses-generating, and no clinical application should be considered before preclinical and clinical validation is performed. It is also plausible that no single receptor may alone explain ICDs development, and that ICD management requires considering multiple molecular targets. Many receptors may interact, both with their individual activity and as heterodimers[70,71], with different receptors being the main responsible in distinct drug classes. Synaptic plasticity, e.g., involving NMDA receptors, may play an important role in habit learning and in the conversion from impulsive to compulsive phenotypes[72]. Finally, not all patients administered with these drugs develop ICDs, and future studies will also need to consider disease factors and patient-related susceptibility.

4.7 Further Directions

Our results are preliminary, and we advocate the use of preclinical and clinical studies to investigate whether and how iatrogenic ICDs arise. In our opinion, to better elucidate these mechanisms, it is necessary to study in vivo effects of 5-HT1a agonists. According with this hypothesis, the use of selective serotonin 5-HT1a receptor biased agonists, still not approved for human use, may be useful to specifically activate intracellular pathways that are only exhibited by dorsal raphe neurons[73], therefore acting only on 5-HT1a plausibly involved in disinhibition. Also, the observation of behavioral changes (e.g., pervasive feeding, hypersexuality) may be more easily referred to impulse control disorders than the many tasks used to investigate impulsivity in isolation-retained animal models[74]. Furthermore, the pharmacovigilance-pharmacodynamic analysis could be extended to epidemiological data (i.e., interpolating occupancy and incidence). Of note, a similar approach was performed on epidemiological data limited to ICDs induced by dopamine agonists and found a potential role of D3 consistent with our results[13]. It would be useful to repeat this study focusing on antipsychotics, possibly assessing personal susceptibility to ICDs before and after drug administration.

4.8 Conclusion

We combined global pharmacovigilance data with receptor occupancies to identify emerging targets associated with drug-induced ICDs. Our results support the role of D3-receptor agonism in inducing ICDs with dopamine receptor agonists used in Parkinson's disease and identified a potential role of 5-HT1a-receptor agonism for antipsychotics.

Antagonism at D1, M3 and M4 receptors may be further investigated as potentially protecting from ICDs by antipsychotics. Further preclinical and clinical studies should investigate whether and how these receptors interact in defining the risk of drug-induced ICDs. Clarifying the mechanistic basis of ICDs may drive drug repurposing and development towards a more effective and safer management.

5. Acknowledgements

Part of the results will be presented at the SIF (Società Italiana di Farmacologia) 2022, to be held in Rome on the 16th-19th of November 2022.

6. Disclosure Statement

Conflict of interest: The authors declare no conflict of interest.

Data availability: The pharmacovigilance data we used comes from the FDA Adverse Event Reporting System, and is made publicly available by the FDA as quarterly data downloadable at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The pharmacokinetic-pharmacodynamic data comes from publicly available sources referred to in the text.

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7. Author contributions

MF, VG, VB, MG, CC, ER, EP conceived the project and confronted with methodological issues. MF, VG, VB, MG wrote the original draft of the manuscript. MF, VG, VB, MG acquired the data. MF, VG preprocessed the data, carried out the analyses and implemented data visualization. CC, ER, EP supervised the project. All the authors read, revised, contributed to the interpretation of results, and approved the final version.

8. Figure legends

Figure 1 Association between activity on D3 and 5-HT1a and reporting of impulse control disorders. Sensitivity analysis b, considering different activities. Linear models were built separately for antipsychotics (above) and dopamine agonists (below). Drugs were color-coded to show their activity. IC (Information Component) 95%CI was shown for each drug.

Figure 2 Pharmacovigilance-pharmacodynamic based hypotheses on iatrogenic ICDs' pathogenesis. Created with BioRender.com

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