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

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

4  
5 **Running title:** Impulse control disorders' pathogenesis  
6

7  
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35

## 36 Abstract

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

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

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

51 **Results:** Among 19,887 reports of impulsivity, 5,898 recorded an antipsychotic, and 3,100 a  
52 dopamine agonist. The more robust signals concerned aripiprazole (N=3,091; median  
53 information component [95% confidence interval] = 4.51[4.45-4.55]) and brexpiprazole (229;  
54 4.00[3.78-4.16]) for antipsychotics, pergolide (105; 5.82[5.50-6.06]) and pramipexole (2009;  
55 5.43[5.36-5.48]) for dopamine agonists. Robust, significant positive associations between drug  
56 occupancy and impulsivity reporting were found for D3 within dopamine agonists (beta=1.52;  
57 p-value=0.047) and 5-HT1a within antipsychotics (1.92, 0.029).

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

62

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

65

## 66 1. Introduction

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

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

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

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

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

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

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

121

## 122 2. Methods

### 123 2.1 Pharmacovigilance Data

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

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

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

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

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

150

## 151 2.2 Pharmacodynamic Data

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

157

$$158 \quad f_{occ} = f([C_r]) = \frac{1}{1 + \frac{K_i}{[C_r]}} \quad \text{[formula 1]}$$

159

$$160 \quad [C_r] = \frac{1000 \times F_u \times C_{max}}{M_r} \quad \text{[formula 2]}$$

161

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

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

180

### 181 2.3 Pharmacovigilance-Pharmacodynamic Models

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



195

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

199 a) Receptor occupancy is considered the best way to approximate drug-receptor activity.  
200 However, given the multiple data required for the calculation, the risk of missing data  
201 is high. Therefore, we used pKi values, instead of occupancy, to decrease the proportion  
202 of missing data.

203 b) Drugs may have different actions on the receptor and may therefore be classified, at  
204 least, as agonist, antagonist, partial agonist, and inverse agonist agents. Thus, an agonist  
205 and an antagonist with the same affinity may have opposite effects. To take this into  
206 account, we reversed the sign of receptor occupancy for antagonist and inverse agonist  
207 drugs. Drugs for which we were not able to retrieve the activity were excluded from  
208 these models.

209 c) Because linear regression models are very sensitive to outliers, we assessed the  
210 robustness of the relationship by excluding outliers from the sensitivity analysis b).

211 d) Finally, following the hypothesis of shared receptors in the development of drug-  
212 induced ICDs, we repeated the sensitivity analysis b) considering antipsychotic and  
213 anti-Parkinson's agents together. We estimated a mixed-effects regression model with  
214 a random intercept for drug class to account for potential differences between  
215 antipsychotic and anti-Parkinson's classes.

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

220

221

## 222 2.4 Statistical tools

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

225

## 226 3. Results

### 227 3.1 Pharmacovigilance Data

228 First, we needed to obtain the measures of disproportionate reporting. We cleaned the  
229 FAERS and retrieved 19,887 ICD reports (0.17%), with pathological gambling and  
230 hypersexuality being the most reported ICD conditions in both antipsychotics and dopamine  
231 agonists (see Figure S1). Antipsychotics were reported in 5,898 (29.66%) ICD reports, with  
232 the three MedDRA preferred terms most reported as reasons for use being bipolar disorder  
233 (1324, 30.98%), major depression (1133, 26.51%), and schizophrenia (939, 21.97%).  
234 Dopamine agonists were reported in 3,100 (15.59%) ICD reports, with the main reasons for  
235 use being Parkinson's disorder (1550, 59.75%), restless leg syndrome (880, 33.92%), and  
236 prolactin-producing pituitary tumor (49, 1.89%). Other drugs reported as primary suspects in  
237 ICD reports were antidepressants (1942, 9.77%), antiepileptics (1325, 6.66%), and  
238 psychostimulants (1213, 6.10%).

239 Within the two populations (i.e., dopamine agonist reports and antipsychotic reports, see  
240 Supplementary Material – Table S2-S3), ICD reports were characterized by a significantly  
241 higher proportion of men (50.58% vs 47.56% in antipsychotics; 59.90% vs 39.46% in  
242 dopamine agonists) and younger age (median[Q1-Q3] = 42 [29-55] years vs 50 [34-64] in  
243 antipsychotics; 56 [48-65] vs 66 [55-75] in dopamine agonists). Lower proportions of deaths  
244 (2.05% vs 12.20% in antipsychotics; 2.42% vs 7.62% in dopamine agonists) and higher of  
245 disability (9.60% vs 1.95%; 4.42% vs 2.26%) were also reported. The onset of ICDs was earlier  
246 for antipsychotics (median[Q1-Q3] = 31 [1-366] days, on 1,871 available time to onset data)  
247 than for dopamine agonists (214 [24-731] days, on 662 available time to onset data).  
248 Dopamine-agonist related ICDs, compared to antipsychotic-related ICDs, also had higher  
249 contribution by men (59.90% vs 50.58%) and older people (56 [48-65] vs 42 [29-55] years  
250 old). Finally, the 254 ICD cases recording the use of both dopamine agonists and antipsychotics  
251 (Table S4) shared the characteristics of ICDs occurring with dopamine agonists (men 60.00%,  
252 age 56 [45-67], but were more similar to ICDs occurring with antipsychotics in the lawyer  
253 contribution (15.29%) and the reported disability rate (8.27%), and the reported hospitalization  
254 rate (42.13%) was substantially higher than when developing ICDs with dopamine agonists  
255 (16.84%) or antipsychotics (32.50%).

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

259 the strongest (i.e., signals with the highest lower extremity of the 95%CI of the IC) being  
260 aripiprazole (N = 3,091; median IC [95%CI] = 4.51[4.45-4.55]), brexpiprazole (N = 229;  
261 4.00[3.78-4.16]), and cariprazine (N = 49; 3.02[2.54-3.36]). On 12 dopamine agonists, 9 with  
262  $\geq 10$  cases, we obtained 9 statistical signals, the strongest being pergolide (N = 105; 5.82[5.50-  
263 6.06]), pramipexole (N = 2009; 5.43[5.36-5.48]), and piribedil (N = 48; 5.01[4.53-5.36]).

264

### 265 3.2 Pharmacodynamic Data

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

275

### 276 3.3 Pharmacovigilance-Pharmacodynamic Models

277 To identify the relationship between each drug receptor occupancy and its ICD  
278 disproportionate reporting, we performed univariate linear regression models (see  
279 Supplementary Material – Table S7) and four sensitivity analyses (see Supplementary Material  
280 – Table S8). In the main analysis, we found two significant positive associations between  
281 occupancy and reporting of ICDs (median IC): 5-HT<sub>1a</sub>-receptor agonism showed a highly  
282 robust positive association with the reporting of ICDs within antipsychotics ( $\beta = 1.924$ ,  $p =$   
283  $0.029$ ,  $R^2 = 0.307$ ); D<sub>3</sub>-receptor agonism showed a robust positive association with the  
284 reporting of ICDs within dopamine agonists ( $\beta = 1.516$ ,  $p = 0.047$ ,  $R^2 = 0.707$ ) (see Figure 1).  
285 Within antipsychotics, we also observed negative associations with antagonism on three  
286 receptors: D<sub>1</sub>-receptor antagonism ( $\beta = -2.511$ ,  $p = 0.014$ ,  $R^2 = 0.603$ ) and M<sub>3</sub>-receptor  
287 antagonism ( $\beta = -2.129$ ,  $p = 0.025$ ,  $R^2 = 0.997$ ) showed to be robust hypotheses at the sensitivity  
288 analyses; M<sub>4</sub>-receptor antagonism ( $\beta = -1.951$ ,  $p = 0.029$ ,  $R^2 = 0.914$ ) showed to be non-robust.

289

## 290 4. Discussion

### 291 4.1 Pathogenetic hypotheses for drug-induced ICDs

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

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

309

### 310 4.2 The potential contribution by D3-receptor agonism

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

318

### 319 4.3 The potential protective role of D1-receptor antagonism

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

322 receptor, particularly localized in the prefrontal area and ventral striatum<sup>10,51</sup>. Since dopamine  
323 activity on D1, activating the direct pathway, physiologically promotes totalizing reward-  
324 driven behaviors, D1-receptor antagonism plausibly suppresses craving and protects against  
325 ICDs.

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

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

337

#### 338 4.4 The potential contribution by 5-HT1a-receptor agonism

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

346 5-HT1a is a G<sub>i</sub>-protein coupled autoreceptor localized in the dorsal raphe that, when  
347 activated, inhibits the serotonergic projections to the ventro tegmental area. Therefore, it may  
348 potentially contribute to the development of ICDs by inhibiting the serotonergic pathway  
349 usually involved in impulse control, resulting in an increased motivational drive. Indeed, its  
350 agonism, particularly at low doses, was observed to induce-reward-driven behaviors<sup>57</sup>; 5-  
351 HT1a-receptor agonism has been found to induce impulsivity in mice<sup>58,59</sup> and rats<sup>60-62</sup>; 5-HT1a-  
352 receptor antagonism reduces impulsivity in rats<sup>63</sup>; 5-HT1A gene polymorphisms bring  
353 susceptibility in humans<sup>64,65</sup>.

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

357

#### 358           4.5 The potential protective role of M3 and M4-receptors antagonism

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

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

385

#### 386 4.6 Strengths and limitations

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

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

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

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

428

#### 429 4.7 Further Directions

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

445

#### 446 4.8 Conclusion

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



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

456

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

460

## 461 6. Disclosure Statement

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

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

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469

## 470 7. Author contributions

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

## 476 8. Figure legends

477

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

481

482  
483

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

484

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