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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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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 addictions¹ (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 untreated², 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 syndrome³, but also with dopamine partial agonists used in
76 schizophrenia and mood disorders^{4,5}. 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 $p=0.008$)⁶, and a pharmacovigilance study on the WHO spontaneous reporting system
80 investigated the association between dopaminergic agents and the reporting of ICDs⁷. 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^{8,9}. 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^{10,11}.

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 ICDs¹². In particular, the D3 receptor, similar to D2 but localized in the
96 ventral striatum, is a preferential target of dopamine agonists¹³. 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 year¹⁴. Furthermore, these
100 hypotheses do not exhaustively explain experimental data. In impulsive rats, the D2 and D3
101 receptors are reduced¹⁵, and a dopamine receptor antagonist can have opposite effects when
102 injected into different portions of the ventral striatum¹⁶. In ICD patients with Parkinson's
103 disease, a gratification-preluding stimulus activates the ventral striatum increasing the release
104 of endogenous dopamine^{17,18} and D3 receptors are reduced in the ventral striatum^{19,20}. 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 management¹⁴, together with the
109 high risk of losing control over Parkinson's symptoms and the possibility of a withdrawal
110 syndrome²¹, 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 addictions²²⁻²⁵ 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 conditions²⁶⁻⁴⁰. 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^{41,42}.

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 stereotypy⁴³ (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 cases⁴⁴. Nonetheless, we set a precautionary
149 threshold of ≥ 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 Neuropsychopharmacology⁴⁵. 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 DrugBank⁴⁶ 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-ChEMBL⁴⁷, and only at last
173 in the Psychoactive Drug Screening Program (PDSP, at
174 <https://pdsp.unc.edu/databases/kidb.php>)⁴⁸. 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 conditions⁴⁹). 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 ≥ 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 ≥ 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_{1a}-receptor agonism showed a highly
282 robust positive association with the reporting of ICDs within antipsychotics ($\beta = 1.924$, $p =$
283 0.029 , $R^2 = 0.307$); D₃-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: D₁-receptor antagonism ($\beta = -2.511$, $p = 0.014$, $R^2 = 0.603$) and M₃-receptor
287 antagonism ($\beta = -2.129$, $p = 0.025$, $R^2 = 0.997$) showed to be robust hypotheses at the sensitivity
288 analyses; M₄-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 targets³³. For example, they were recently applied to investigate the
296 pathogenesis of antipsychotic-induced hyponatremia³⁴, pneumonia²⁷, diabetes³⁵,
297 Parkinsonism³⁷. 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 practice¹³,
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 striatum⁵⁰. 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^{10,51}. 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 ICDs⁵².
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 D1⁵¹. Other polymorphisms in DRD1 have been linked to ICDs,
332 neuropsychiatric disease, problem gambling, addiction, and cognitive functioning in non-PD
333 populations^{53,54}.

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 unclear⁵⁵. 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 receptor⁵⁶.

346 5-HT1a is a G_i-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 behaviors⁵⁷; 5-
351 HT1a-receptor agonism has been found to induce impulsivity in mice^{58,59} and rats⁶⁰⁻⁶²; 5-HT1a-
352 receptor antagonism reduces impulsivity in rats⁶³; 5-HT1A gene polymorphisms bring
353 susceptibility in humans^{64,65}.

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 behaviors⁶⁶. The laterodorsal and
365 pedunculopontine neurons, in particular, contribute with cholinergic input that, through the
366 post-synaptic muscarinic G_q-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_i-protein coupled receptor M4, which reduces acetylcholine release, and
369 therefore contrasts the acetylcholine-mediated activation of GABAergic neurons⁶⁷. 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 mice⁶⁷, muscarinic receptor antagonism has shown fewer risk-
380 taking behaviors in rats⁶⁸, and mice lacking M4 in cholinergic receptors were unable to learn
381 positive reinforcement⁶⁹. 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 numbers⁴⁴, 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^{70,71}, 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 phenotypes⁷². 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 neurons⁷³, 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 models⁷⁴. 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 results¹³. 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

9. References

- 486 1. Weintraub D. Impulse control disorders in Parkinson's disease: A 20-year odyssey. *Mov*
487 *Disord.* 2019; 34: 447–52.
- 488 2. Lopez AM, Weintraub D, Claassen DO. Impulse Control Disorders and Related
489 Complications of Parkinson's Disease Therapy. *Semin Neurol.* 2017; 37: 186–92.
- 490 3. Grall-Bronnec M, Victorri-Vigneau C, Donnio Y, Leboucher J, Rousselet M, Thiabaud E,
491 et al. Dopamine Agonists and Impulse Control Disorders: A Complex Association. *Drug*
492 *Saf.* 2018; 41: 19–75.
- 493 4. Fusaroli M, Raschi E, Giunchi V, Menchetti M, Rimondini Giorgini R, De Ponti F, et al.
494 Impulse Control Disorders by Dopamine Partial Agonists: A Pharmacovigilance-
495 Pharmacodynamic Assessment through the FDA Adverse Event Reporting System. *Int J*
496 *Neuropsychopharmacol.* 2022; : pyac031.
- 497 5. Zazu L, Morera-Herrerias T, Garcia M, Aguirre C, Unax L. Do cariprazine and
498 brexpiprazole cause impulse control symptoms? A case/non-case study. *European*
499 *Neuropsychopharmacology.* 2021; 50: 107–11.
- 500 6. Wolfschlag M, Håkansson A. Increased risk for developing gambling disorder under the
501 treatment with pramipexole, ropinirole, and aripiprazole: A nationwide register study
502 in Sweden. *PLOS ONE.* 2021; 16: e0252516.
- 503 7. De Wit LE, Wilting I, Souverein PC, van der Pol P, Egberts TCG. Impulse control
504 disorders associated with dopaminergic drugs: A disproportionality analysis using
505 vigibase. *European Neuropsychopharmacology.* 2022; 58: 30–8.
- 506 8. Beaulieu J-M, Gainetdinov RR. The physiology, signaling, and pharmacology of
507 dopamine receptors. *Pharmacol. Rev.* 2011; 63: 182–217.
- 508 9. Soares-Cunha C, Coimbra B, Sousa N, Rodrigues AJ. Reappraising striatal D1- and D2-
509 neurons in reward and aversion. *Neurosci Biobehav Rev.* 2016; 68: 370–86.
- 510 10. Tsai H-C, Zhang F, Adamantidis A, Stuber GD, Bonci A, de Lecea L, et al. Phasic firing in
511 dopaminergic neurons is sufficient for behavioral conditioning. *Science.* 2009; 324:
512 1080–4.
- 513 11. Dreyer JK, Herrik KF, Berg RW, Hounsgaard JD. Influence of Phasic and Tonic Dopamine
514 Release on Receptor Activation. *J. Neurosci.* 2010; 30: 14273–83.
- 515 12. Voon V, Fox SH. Medication-related impulse control and repetitive behaviors in
516 Parkinson disease. *Arch. Neurol.* 2007; 64: 1089–96.
- 517 13. Seeman P. Parkinson's disease treatment may cause impulse-control disorder via
518 dopamine D3 receptors. *Synapse.* 2015; 69: 183–9.

- 519 14. Corvol J-C, Artaud F, Cormier-Dequaire F, Rascol O, Durif F, Derkinderen P, et al.
520 Longitudinal analysis of impulse control disorders in Parkinson disease. *Neurology*.
521 2018; 91: e189–201.
- 522 15. Dalley JW, Fryer TD, Brichard L, Robinson ESJ, Theobald DEH, Lääne K, et al. Nucleus
523 Accumbens D2/3 Receptors Predict Trait Impulsivity and Cocaine Reinforcement.
524 *Science*. 2007; 315: 1267–70.
- 525 16. Besson M, Belin D, McNamara R, Theobald DE, Castel A, Beckett VL, et al. Dissociable
526 Control of Impulsivity in Rats by Dopamine D2/3 Receptors in the Core and Shell
527 Subregions of the Nucleus Accumbens. *Neuropsychopharmacology*. 2010; 35: 560–9.
- 528 17. Martini A, Dal Lago D, Edelstyn NMJ, Salgarello M, Lugoboni F, Tamburin S.
529 Dopaminergic Neurotransmission in Patients With Parkinson’s Disease and Impulse
530 Control Disorders: A Systematic Review and Meta-Analysis of PET and SPECT Studies.
531 *Front Neurol*. 2018; 9.
- 532 18. Politis M, Loane C, Wu K, O’Sullivan SS, Woodhead Z, Kiferle L, et al. Neural response to
533 visual sexual cues in dopamine treatment-linked hypersexuality in Parkinson’s disease.
534 *Brain*. 2013; 136: 400–11.
- 535 19. Barbosa P, Hapuarachchi B, Djamshidian A, Strand K, Lees AJ, de Silva R, et al. Reply to
536 “Impulse control disorders are associated with lower ventral striatum dopamine D3
537 receptor availability in Parkinson’s disease: A [11C]-PHNO PET study.” *Parkinsonism
538 Relat Disord*. 2021; 93: 31–2.
- 539 20. Pagano G, Molloy S, Bain PG, Rabiner EA, Ray Chaudhuri K, Brooks DJ, et al. Impulse
540 control disorders are associated with lower ventral striatum dopamine D3 receptor
541 availability in Parkinson’s disease: A [11C]-PHNO PET study. *Parkinsonism Relat Disord*.
542 2021; 90: 52–6.
- 543 21. Yu XX, Fernandez HH. Dopamine agonist withdrawal syndrome: A comprehensive
544 review. *Journal of the Neurological Sciences*. 2017; 374: 53–5.
- 545 22. Bock R, Shin JH, Kaplan AR, Dobi A, Markey E, Kramer PF, et al. Strengthening the
546 accumbal indirect pathway promotes resilience to compulsive cocaine use. *Nature
547 Neuroscience*. 2013; 16: 632–8.
- 548 23. Browne CJ, Abela AR, Chu D, Li Z, Ji X, Lambe EK, et al. Dorsal raphe serotonin neurons
549 inhibit operant responding for reward via inputs to the ventral tegmental area but not
550 the nucleus accumbens: evidence from studies combining optogenetic stimulation and
551 serotonin reuptake inhibition. *Neuropsychopharmacol*. 2019; 44: 793–804.
- 552 24. Miyazaki KW, Miyazaki K, Doya K. Activation of the central serotonergic system in
553 response to delayed but not omitted rewards. *The European Journal of Neuroscience*.
554 2011; 33: 153–60.
- 555 25. Polter AM, Kauer JA. Stress and VTA synapses: Implications for addiction and
556 depression. *Eur J Neurosci*. 2014; 39: 1179–88.

- 557 26. Carnovale C, Mazhar F, Arzenton E, Moretti U, Pozzi M, Mosini G, et al. Bullous
558 pemphigoid induced by dipeptidyl peptidase-4 (DPP-4) inhibitors: a pharmacovigilance-
559 pharmacodynamic/pharmacokinetic assessment through an analysis of the vigibase®.
560 *Expert Opin Drug Saf.* 2019; 18: 1099–108.
- 561 27. Cepaityte D, Siafis S, Egberts T, Leucht S, Kouvelas D, Papazisis G. Exploring a Safety
562 Signal of Antipsychotic-Associated Pneumonia: A Pharmacovigilance-Pharmacodynamic
563 Study. *Schizophr Bull.* 2021; 47: 672–81.
- 564 28. Çiray RO, Halaç E, Turan S, Tunçtürk M, Özbek M, Ermiş Ç. Selective serotonin reuptake
565 inhibitors and manic switch: A pharmacovigilance and pharmacodynamical study. *Asian*
566 *J Psychiatr.* 2021; 66: 102891.
- 567 29. Cornet L, Khouri C, Roustit M, Guignabert C, Chaumais M-C, Humbert M, et al.
568 Pulmonary arterial hypertension associated with protein kinase inhibitors: a
569 pharmacovigilance-pharmacodynamic study. *Eur. Respir. J.* 2019; 53.
- 570 30. De Bruin ML, Pettersson M, Meyboom RHB, Hoes AW, Leufkens HGM. Anti-HERG
571 activity and the risk of drug-induced arrhythmias and sudden death. *Eur Heart J.* 2005;
572 26: 590–7.
- 573 31. Lapeyre-Mestre M, Montastruc F. Interest of pharmacoepidemiology for
574 pharmacodynamics and analysis of the mechanism of action of drugs. *Therapie.* 2019;
575 74: 209–14.
- 576 32. Mahé J, de Campaigno EP, Chené A-L, Montastruc J-L, Despas F, Jolliet P. Pleural
577 adverse drugs reactions and protein kinase inhibitors: Identification of suspicious
578 targets by disproportionality analysis from VigiBase. *Br J Clin Pharmacol.* 2018; 84:
579 2373–83.
- 580 33. Mazhar F, Pozzi M, Gentili M, Scatigna M, Clementi E, Radice S, et al. Association of
581 Hyponatraemia and Antidepressant Drugs: A Pharmacovigilance-Pharmacodynamic
582 Assessment Through an Analysis of the US Food and Drug Administration Adverse
583 Event Reporting System (FAERS) Database. *CNS Drugs.* 2019; 33: 581–92.
- 584 34. Mazhar F, Battini V, Pozzi M, Invernizzi E, Mosini G, Gringeri M, et al. Hyponatremia
585 Following Antipsychotic Treatment: In Silico Pharmacodynamics Analysis of
586 Spontaneous Reports From the US Food and Drug Administration Adverse Event
587 Reporting System Database and an Updated Systematic Review. *Int J*
588 *Neuropsychopharmacol.* 2021; 24: 477–89.
- 589 35. Montastruc F, Palmaro A, Bagheri H, Schmitt L, Montastruc J-L, Lapeyre-Mestre M. Role
590 of serotonin 5-HT_{2C} and histamine H₁ receptors in antipsychotic-induced diabetes: A
591 pharmacoepidemiological-pharmacodynamic study in VigiBase. *European*
592 *Neuropsychopharmacology.* 2015; 25: 1556–65.
- 593 36. Montastruc J-L, Rousseau V, de Canecaude C, Roussin A, Montastruc F. Role of
594 serotonin and norepinephrine transporters in antidepressant-induced arterial

- 595 hypertension: a pharmacoepidemiological-pharmacodynamic study. *Eur J Clin*
596 *Pharmacol.* 2020; 76: 1321–7.
- 597 37. Nguyen TTH, Pariente A, Montastruc J-L, Lapeyre-Mestre M, Rousseau V, Rascol O, et
598 al. An original pharmacoepidemiological-pharmacodynamic method: application to
599 antipsychotic-induced movement disorders. *Br J Clin Pharmacol.* 2017; 83: 612–22.
- 600 38. Nguyen TTH, Roussin A, Rousseau V, Montastruc J-L, Montastruc F. Role of Serotonin
601 Transporter in Antidepressant-Induced Diabetes Mellitus: A Pharmacoepidemiological-
602 Pharmacodynamic Study in VigiBase®. *Drug Saf.* 2018; 41: 1087–96.
- 603 39. Patras de Campaigno E, Bondon-Guitton E, Laurent G, Montastruc F, Montastruc J-L,
604 Lapeyre-Mestre M, et al. Identification of cellular targets involved in cardiac failure
605 caused by PKI in oncology: an approach combining pharmacovigilance and
606 pharmacodynamics. *Br J Clin Pharmacol.* 2017; 83: 1544–55.
- 607 40. Sifakis S, Papazisis G. Detecting a potential safety signal of antidepressants and type 2
608 diabetes: a pharmacovigilance-pharmacodynamic study. *Br J Clin Pharmacol.* 2018; 84:
609 2405–14.
- 610 41. Gaimari A, Fusaroli M, Raschi E, Baldin E, Vignatelli L, Nonino F, et al. Amyotrophic
611 Lateral Sclerosis as an Adverse Drug Reaction: A Disproportionality Analysis of the Food
612 and Drug Administration Adverse Event Reporting System. *Drug Saf.* 2022; 45: 663–73.
- 613 42. Fusaroli M, Isgrò V, Cutroneo PM, Ferrajolo C, Cirillo V, Del Bufalo F, et al. Post-
614 Marketing Surveillance of CAR-T-Cell Therapies: Analysis of the FDA Adverse Event
615 Reporting System (FAERS) Database. *Drug Saf.* 2022; [Cited 2022 Jul 16] Available from
616 <https://doi.org/10.1007/s40264-022-01194-z>
- 617 43. Fusaroli M, Raschi E, Contin M, Sambati L, Menchetti M, Fioritti A, et al. Impulsive
618 Conditions in Parkinson’s Disease: a pharmacosurveillance-supported list. *Parkinsonism*
619 *& Related Disorders.* 2021; 90: 79–83.
- 620 44. Norén GN, Hopstadius J, Bate A. Shrinkage observed-to-expected ratios for robust and
621 transparent large-scale pattern discovery. *Stat Methods Med Res.* 2013; 22: 57–69.
- 622 45. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al.
623 Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology:
624 Update 2017. *Pharmacopsychiatry.* 2018; 51: 9–62.
- 625 46. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, et al. DrugBank 5.0: a major
626 update to the DrugBank database for 2018. *Nucleic Acids Research.* 2018; 46: D1074–
627 82.
- 628 47. Mendez D, Gaulton A, Bento AP, Chambers J, De Veij M, Félix E, et al. ChEMBL: towards
629 direct deposition of bioassay data. *Nucleic Acids Research.* 2019; 47: D930–40.

- 630 48. Besnard J, Ruda GF, Setola V, Abecassis K, Rodriguiz RM, Huang X-P, et al. Automated
631 design of ligands to polypharmacological profiles. *Nature*. 2012; 492:
632 10.1038/nature11691.
- 633 49. American Psychiatric Association. DSM-IV Impulse-Control Disorders Not Elsewhere
634 Classified. In: DSM-IV. American Psychiatric Association; 2000. p. 663–77.
- 635 50. Gurevich EV, Joyce JN. Distribution of dopamine D3 receptor expressing neurons in the
636 human forebrain: comparison with D2 receptor expressing neurons.
637 *Neuropsychopharmacology*. 1999; 20: 60–80.
- 638 51. Erga AH, Dalen I, Ushakova A, Chung J, Tzoulis C, Tysnes OB, et al. Dopaminergic and
639 Opioid Pathways Associated with Impulse Control Disorders in Parkinson’s Disease.
640 *Frontiers in Neurology*. 2018; 9. [Cited 2022 Jul 6] Available from
641 <https://www.frontiersin.org/articles/10.3389/fneur.2018.00109>
- 642 52. Augustine A, Winstanley CA, Krishnan V. Impulse Control Disorders in Parkinson’s
643 Disease: From Bench to Bedside. *Frontiers in Neuroscience*. 2021; 15. [Cited 2022 Jul 6]
644 Available from <https://www.frontiersin.org/articles/10.3389/fnins.2021.654238>
- 645 53. Comings DE, Gade R, Wu S, Chiu C, Dietz G, Muhleman D, et al. Studies of the potential
646 role of the dopamine D1 receptor gene in addictive behaviors. *Mol Psychiatry*. 1997; 2:
647 44–56.
- 648 54. Huang W, Ma JZ, Payne TJ, Beuten J, Dupont RT, Li MD. Significant association of DRD1
649 with nicotine dependence. *Hum Genet*. 2008; 123: 133–40.
- 650 55. Kranz GS, Kasper S, Lanzenberger R. Reward and the serotonergic system.
651 *Neuroscience*. 2010; 166: 1023–35.
- 652 56. Liu Z, Lin R, Luo M. Reward Contributions to Serotonergic Functions. *Annu Rev*
653 *Neurosci*. 2020; 43: 141–62.
- 654 57. Hayes DJ, Greenshaw AJ. 5-HT receptors and reward-related behaviour: a review.
655 *Neurosci Biobehav Rev*. 2011; 35: 1419–49.
- 656 58. Chu J, Deyama S, Li X, Motono M, Otda A, Saito A, et al. Role of 5-HT1A receptor-
657 mediated serotonergic transmission in the medial prefrontal cortex in acute restraint
658 stress-induced augmentation of rewarding memory of cocaine in mice. *Neurosci Lett*.
659 2021; 743: 135555.
- 660 59. Humby T, Smith GE, Small R, Davies W, Carter J, Bentley CA, et al. Effects of 5-HT2C, 5-
661 HT1A receptor challenges and modafinil on the initiation and persistence of gambling
662 behaviours. *Psychopharmacology (Berl)*. 2020; 237: 1745–56.
- 663 60. Lu C-L, Ku Y-C, Lo S-M, Peng C-H, Tung C-S, Lin Y-W, et al. Acute and subchronic effects
664 of buspirone on attention and impulsivity in the five-choice serial reaction time task in
665 rats. *Neurosci Lett*. 2013; 556: 210–5.

- 666 61. Liu YP, Wilkinson LS, Robbins TW. Effects of acute and chronic buspirone on impulsive
667 choice and efflux of 5-HT and dopamine in hippocampus, nucleus accumbens and
668 prefrontal cortex. *Psychopharmacology (Berl)*. 2004; 173: 175–85.
- 669 62. Martis L-S, Højgaard K, Holmes MC, Elfving B, Wiborg O. Vortioxetine ameliorates
670 anhedonic-like behaviour and promotes strategic cognitive performance in a rodent
671 touchscreen task. *Sci Rep*. 2021; 11: 9113.
- 672 63. Ohmura Y, Kumamoto H, Tsutsui-Kimura I, Minami M, Izumi T, Yoshida T, et al.
673 Tansospirone suppresses impulsive action by possible blockade of the 5-HT1A
674 receptor. *J Pharmacol Sci*. 2013; 122: 84–92.
- 675 64. Benko A, Lazary J, Molnar E, Gonda X, Tothfalusi L, Pap D, et al. Significant association
676 between the C(-1019)G functional polymorphism of the HTR1A gene and impulsivity.
677 *Am J Med Genet B Neuropsychiatr Genet*. 2010; 153B: 592–9.
- 678 65. Stamatis CA, Engelmann JB, Ziegler C, Domschke K, Hasler G, Timpano KR. A
679 neuroeconomic investigation of 5-HTT/5-HT1A gene variation, social anxiety, and risk-
680 taking behavior. *Anxiety Stress Coping*. 2020; 33: 176–92.
- 681 66. Jhou TC. The rostromedial tegmental (RMTg) “brake” on dopamine and behavior: A
682 decade of progress but also much unfinished work. *Neuropharmacology*. 2021; 198:
683 108763.
- 684 67. Buie N, Sodha D, Scheinman SB, Steidl S. Rewarding effects of M4 but not M3
685 muscarinic cholinergic receptor antagonism in the rostromedial tegmental nucleus.
686 *Behav Brain Res*. 2020; 379: 112340.
- 687 68. Betts GD, Hynes TJ, Winstanley CA. Pharmacological evidence of a cholinergic
688 contribution to elevated impulsivity and risky decision-making caused by adding win-
689 paired cues to a rat gambling task. *J Psychopharmacol*. 2021; 35: 701–12.
- 690 69. Klawonn AM, Wilhelms DB, Lindström SH, Singh AK, Jaarola M, Wess J, et al. Muscarinic
691 M4 Receptors on Cholinergic and Dopamine D1 Receptor-Expressing Neurons Have
692 Opposing Functionality for Positive Reinforcement and Influence Impulsivity. *Frontiers*
693 *in Molecular Neuroscience*. 2018; 11. [Cited 2022 May 15] Available from
694 <https://www.frontiersin.org/article/10.3389/fnmol.2018.00139>
- 695 70. Anastasio NC, Stutz SJ, Fink LHL, Swinford-Jackson SE, Sears RM, DiLeone RJ, et al.
696 Serotonin (5-HT) 5-HT2A Receptor (5-HT2AR):5-HT2CR Imbalance in Medial Prefrontal
697 Cortex Associates with Motor Impulsivity. *ACS Chem. Neurosci*. 2015; 6: 1248–58.
- 698 71. Bono F, Mutti V, Fiorentini C, Missale C. Dopamine D3 Receptor Heteromerization:
699 Implications for Neuroplasticity and Neuroprotection. *Biomolecules*. 2020; 10: 1016.
- 700 72. Wang LP, Li F, Wang D, Xie K, Wang D, Shen X, et al. NMDA receptors in dopaminergic
701 neurons are crucial for habit learning. *Neuron*. 2011; 72: 1055–66.

- 702 73. Becker G, Bolbos R, Costes N, Redouté J, Newman-Tancredi A, Zimmer L. Selective
703 serotonin 5-HT_{1A} receptor biased agonists elicit distinct brain activation patterns: a
704 pharmacMRI study. *Sci Rep.* 2016; 6: 26633.
- 705 74. Esteves M, Moreira PS, Sousa N, Leite-Almeida H. Assessing Impulsivity in Humans and
706 Rodents: Taking the Translational Road. *Frontiers in Behavioral Neuroscience.* 2021; 15.
- 707