

# The Dopamine Receptor D<sub>3</sub> and Pramipexole: from Parkinson Disease to Pathological Gambling

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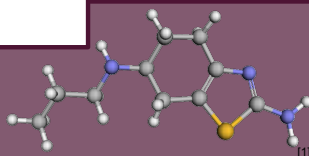
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## Introduction

Parkinson Disease (PD) is a progressive neurodegeneration that causes motor impairment. This results from the death of dopaminergic neurons and the consequent depletion of dopamine in the striatum.

Dopamine replacement therapies include levodopa and dopamine agonists (DAs). The latter are competent and commonly prescribed drugs; Pramipexole is one of them.

Pramipexole is effective and alleviates the motor symptoms of PD but it has been associated with the development of Impulse Control Disorders (ICDs). These comprise several psychiatric disorders characterized by impulsivity, failure to resist temptations and inability to learn from negative outcomes.



## Aims

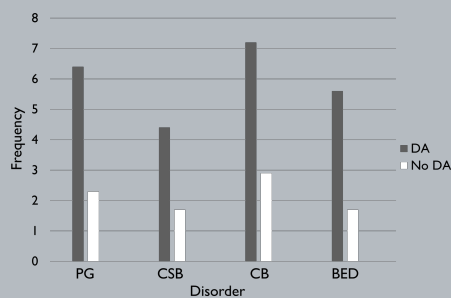
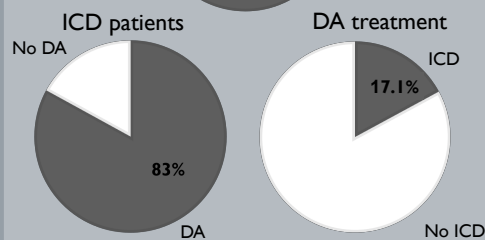
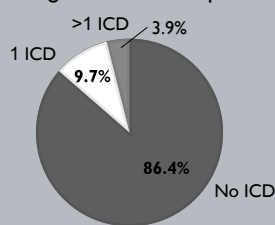
- To find results that depict the percentage of patients who develop Impulse Control Disorders, which of them were pramipexole-treated patients and which are the most frequent ICDs.
- To find results that determine the binding affinity of pramipexole to the D<sub>3</sub> receptor, in comparison to other dopamine agonists and other receptors.
- To find results that demonstrate the localization of the D<sub>3</sub> dopamine receptor to limbic areas of the brain.

## Materials & Methods

### Frequency of ICDs. Cross-sectional study

3090 PD patients under treatment >1year  
Evaluation of pathological gambling, compulsive sexual behavior, compulsive buying and binge-eating disorder

### ICD diagnosis in overall patients



420/3090 patients (13.6%) diagnosed with ICD.  
↳ 120 patients ≥ 2 ICD, 300 = 1 ICD

83% of ICD patients under treatment with a DA.  
17.1% of the patients taking a dopamine agonist developed ICDs.

All types of ICDs are more frequent in dopamine agonist-treated patients.

### Radioligand binding assays

[<sup>3</sup>H]pramipexole and [<sup>3</sup>H]spiperone

## Results

### 1. Competition assay using [<sup>3</sup>H]spiperone

Dissociation constant	D <sub>2L</sub>	D <sub>3</sub>
K <sub>H</sub> (nM)	2.07±0.32	0.49±0.09
K <sub>L</sub> (nM)	139±32	2.78±0.45
K <sub>GppNHp</sub> (nM)	701±49	2.4±0.09

### 2. Saturation assay using [<sup>3</sup>H]pramipexole

	K <sub>D</sub> (nM)	B <sub>max</sub> (pmol/mg)
D <sub>2L</sub>	1.26±0.25	0.70±0.22
D <sub>2S</sub>	0.96±0.13	0.58±0.06
D <sub>3</sub>	0.22±0.03	3.00±1.00

### 3. Indirect competition assay using ↓ [<sup>3</sup>H]pramipexole

K <sub>i</sub> (nM)	D <sub>2L</sub>	D <sub>2S</sub>	D <sub>3</sub>
Pramipexole	3.9±0.2	3.3±0.3	0.5±0.1
Bromocriptine	2.5±0.4	4.8±0.8	12.2±1.7
Quinpirole	1.8±0.3	1.5±0.1	0.96±0.03

1. Pramipexole has a clear preference for the binding to D<sub>3</sub>, when compared to one of the isoforms of the D<sub>2</sub> receptor.

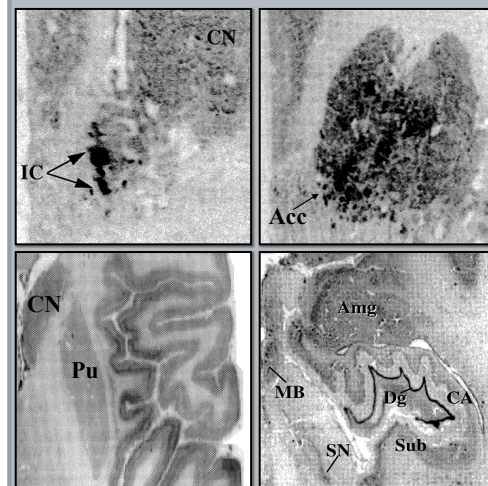
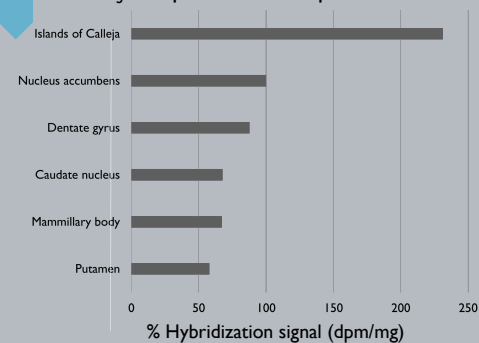
2. Two populations of binding sites with significantly different affinities at the D<sub>3</sub> receptor.  
D<sub>3</sub>B<sub>max</sub> > D<sub>2</sub>B<sub>max</sub> → D<sub>3</sub> more binding capacity  
D<sub>2</sub>K<sub>d</sub> ≈ 5.7 D<sub>3</sub>K<sub>d</sub>(high) and more affinity

3. D<sub>2</sub>K<sub>i</sub> ≈ 7D<sub>3</sub>K<sub>i</sub> → High selectivity of pramipexole for D<sub>3</sub>  
Pramipexole has the greatest binding affinity at D<sub>3</sub>, when compared to other DAs

### Localization of the D<sub>3</sub> dopamine receptor

In situ hybridization histochemistry  
Human D<sub>3</sub> receptor cDNA  
Nissl staining

### D<sub>3</sub> receptor mRNA expression



Abbreviations: IC: islands of Calleja. Acc: nucleus accumbens, CN: caudate nucleus, Pu: putamen, MB: mammillary body, Dg: dentate gyrus.

↑↑↑D<sub>3</sub> expression in areas that are part of or associated with the limbic system.  
↓ D<sub>3</sub> expression in areas related to motor function.  
Dual localization → D<sub>3</sub> involved in both behavioral and motor functions

## Conclusions

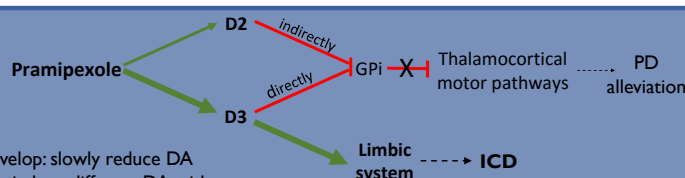
There is a clear association between DA treatment and ICD. This must be recognized as early as possible due to adverse personal and financial consequences.

Before starting a pramipexole treatment:

- Consider risk factors (early PD onset, novelty seeking, hypomania, impaired planning, family history of alcohol abuse). [5]
- Evaluate risk/benefit ratio.
- Adjust dose and therapy to each case.

If ICD develop: slowly reduce DA dose or switch to different DA with lower affinity for the D<sub>3</sub> receptor

Future: elucidate the exact molecular mechanism responsible for the convergence of PD and ICD, as it is not clear yet.  
Further functional imaging studies and genome wide association studies. [6]



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