Nouvelles avenues thérapeutiques pour la maladie de Parkinson

Symposium de Recherche Saucier – van Berkom 2021

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McGill

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neuro

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Déclaration

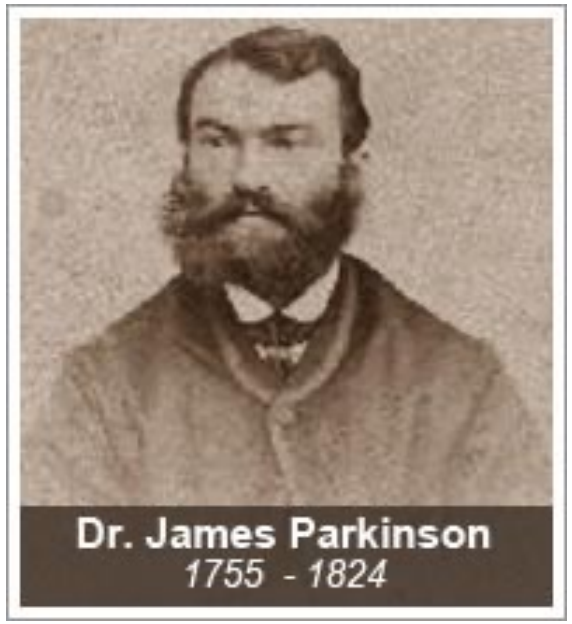
- Neurodiem

Plan de la présentation

- Bref historique
- Les hallucinations dans la maladie de Parkinson
- Les causes
- Les traitements
- Nouvelles avenues thérapeutiques

Historique

- Décrite par James Parkinson en 1817, un médecin britannique
  - *An Essay on the Shaking Palsy*
  - Avait observé 6 individus dans les rues de Londres
  - N'avait pas examiné les patients ni pratiqué d'autopsie; croyait que la lésion se situait dans le tronc cérébral et la moelle



Historique

AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.

1817.

L

AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (*Paralysis Agitans.*)

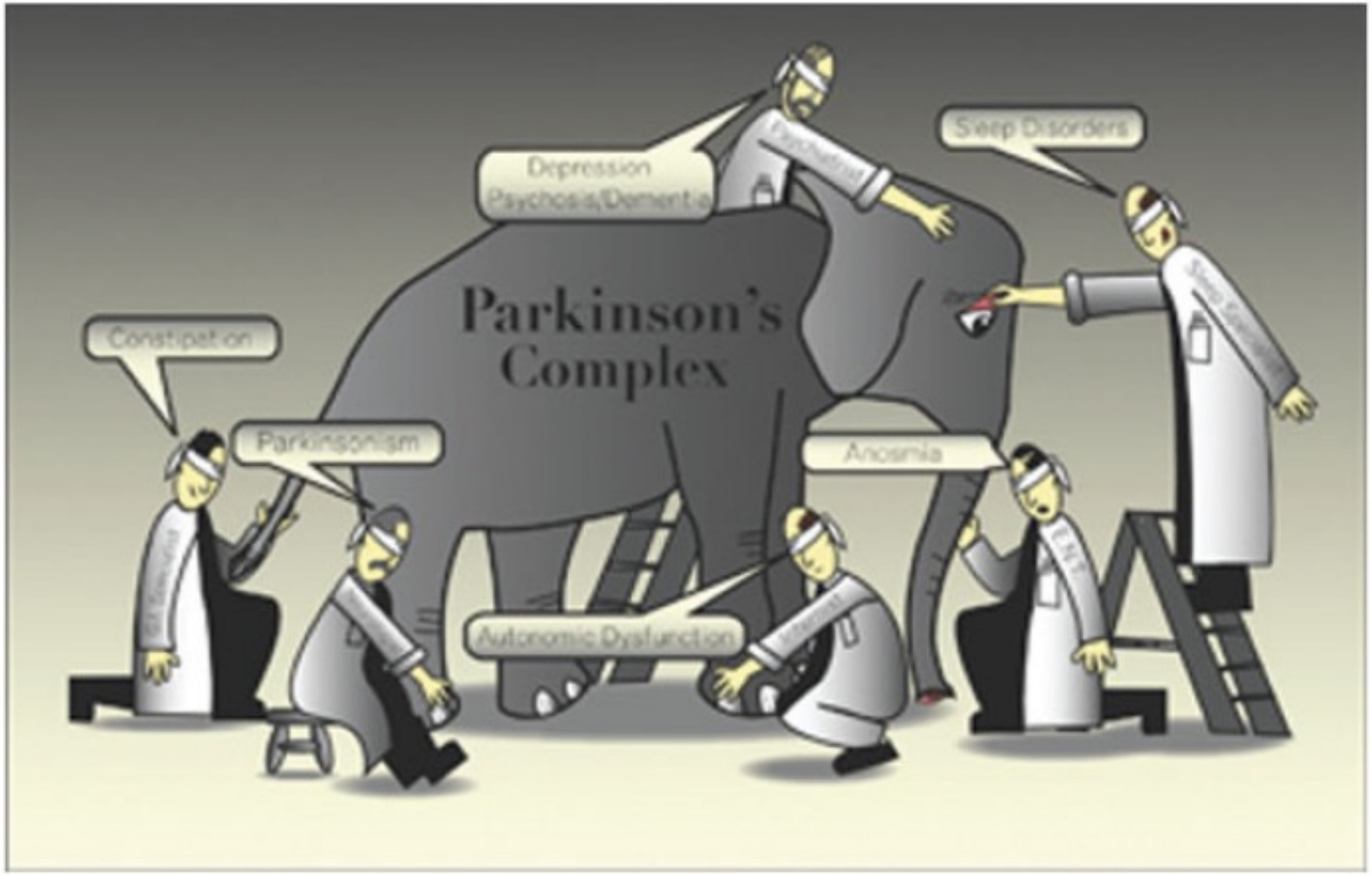
Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

THE term Shaking Palsy has been vaguely employed by medical writers in general. By some it has been used to designate or-

Historique

Gowers 1886

Maladie de Parkinson – au-delà des symptômes moteurs



Langston. Ann Neurol 2006

Épidémiologie

Movement Disorders
Vol. 20, No. 2, 2005, pp. 190–199

Sydney Multicenter Study of Parkinson's Disease: Non-L-Dopa–Responsive Problems Dominate at 15 Years

Mariese A. Hely, MBBS,[1]* John G.L. Morris, MD,[1] Wayne G.J. Reid, Robert Trafficante, BAppScMaths[2]

Abstract: One-third of the 149 people recruited 15 to 18 years ago in the Sydney Multicentre Study of Parkinson's disease have survived. The original study compared low-dose levodopa with low-dose bromocriptine. We now report the problems experienced by people who survive 15 years from diagnosis. The standardized mortality ratio is significantly elevated at 1.86 and is not significantly different between treatment arms. Falls occur in 81% of patients, and 23% sustained fractures. Cognitive decline is present in 84%, and 48% fulfill the criteria for dementia. Hallucinations and depression are experienced by 50%. Choking has occurred in 50%, symptomatic postural hypotension in 35%, and urinary incontinence in 41%. No patient is still employed, and 40% of patients live in aged care facilities. Although approximately 95% have experienced L-dopa–induced dyskinesia/dystonia and end of dose failure of

Qu’est-ce qu’une hallucination?

- Hallucination
  - Perception d’un objet non réel
- Illusion
  - Interprétation erronée d’une donnée sensorielle
- Délire
  - Perte du sens de la réalité se traduisant par un ensemble de convictions fausses, irrationnelles, auxquelles le sujet adhère de façon inébranlable

Larousse

Quel type d'hallucinations?

- Visuelles
- Auditives
- Olfactives
- Gustatives
- Tactiles
- Multimodales

Goetz *et al*. Mov Disord 2011

Caractéristiques des hallucinations visuelles

Characteristic	*Patient No*	*%*
Frequency:		
Daily	6	23.1
2–4 times/week	6	23.1
Once a week	9	34.6
Don't know	5	19.2
Size:		
Normal	12	46.2
Miniaturised	9	34.6
Don't know	5	19.2
Transparency:		
Solid	25	96.2
Transparent	1	3.8
Movement:		
Moves	7	26.9
Still	17	65.4
Varies	2	7.7
Content		
People	15	57.7
Animals	7	26.9
Objects	8	30.8
Can't describe	2	7.7
Multiple content	19	73.1
Single content	5	19.2
Can't describe	2	7.7
Familiarity of content:		
Familiar	6	23
Unfamiliar	18	69.2
Unknown	2	7.7
Duration:		
Minutes	2	7.7
Hours	8	30.8
Days	2	7.7
Varies	10	38.5

Holroyd *et al*. J Neurol Neurosurg Psychiatry 2001

Est-ce que mes médicaments causent les hallucinations?

- C’est compliqué

Est-ce que mes médicaments causent les hallucinations?

Table 3 Comparison of hallucinators v non-hallucinators

	Visual hallucinations (n=26)		*No hallucinations (n=72)*		
	Mean (SD)	*n (%)*	*Mean (SD)*	*n (%)*	*Statistical analysis*
TICS	29.9 (5.8)		33.0 (3.5)		$t=-3.22$, df=95, p=0.002
Visual acuity best eye 20/	20/44.6 (36.6)		20/32.8 (12.1)		$t=2.42$, df=95, p=0.018
GDS	7.9 (6.5)		5.0 (4.5)		$t=2.50$, df=95, p=0.014
UPDRS	47.8 (21.4)		38.5 (16.5)		$t=2.22$, df=91, p=0.03
Total levodopa dose (mg/d)	648.1 (533.9)		593.1 (497.9)		$t=0.47$, df=96, p=0.63
Years of levodopa treatment	9.2 (4.3)		7.4 (4.7)		$t=1.63$, df=79, p=0.11
No of medications	4.6 (2.0)		4.0 (2.1)		$t=1.20$, df=91, p=0.23
Personal psychiatric history:					
Yes		9 (34.6)		19 (26.4)	Fisher's exact test
No		17 (65.4)		53 (73.6)	p=0.30
Levodopa use:					
Yes		22 (84.6)		60 (83.3)	Fisher's exact test
No		4 (15.4)		12 (16.7)	p=1.0
Anticholinergic use:					
Yes		5 (19.2)		10 (14.1)	Fisher's exact test
No		21 (80.8)		61 (85.9)	p=0.54
Amantadine use:					
Yes		4 (15.4)		5 (7.0)	Fisher's exact test
No		22 (84.6)		66 (93.0)	p=0.24
Dopamine agonist use:					
Yes		10 (38.5)		17 (24.3)	Fisher's exact test
No		16 (61.5)		53 (75.7)	p=0.21
Selegilene use:					
Yes		16 (61.5)		35 (49.3)	Fisher's exact test
No		10 (38.5)		36 (50.7)	p=0.36

TICS=Telephone interview for cognitive status; GDS=geriatric depression scale; UPDRS=unified Parkinson's disease rating scale.

Holroyd *et al*. J Neurol Neurosurg Psychiatry 2001

Est-ce que mes médicaments causent les hallucinations?

Table 2. Relationship between drug profile and the development of hallucinations (patients already on l-dopa treatment N = 348). Hazard ratios and 95% CI

Drug	Number of patients	Hazard ratio (95% CI)	P value
Amantadine	102	1.06 (0.67–1.67)	0.792
Entacapone	56	1.02 (0.58–1.82)	0.938
Deprenyl	181	1.04 (0.57–1.88)	0.908
Pergolide	67	0.94 (0.56–1.56)	0.798
Ropinirole	62	0.87 (0.45–1.68)	0.682
Anticholinergic (Biperiden, Trihexyphenidyl)	42	0.94 (0.5–1.78)	0.850

Adjusted to disease related factors: age at PD diagnosis, disease duration and the presence of dementia

Merims *et al*. J Neural Transm 2004

Est-ce que mes médicaments causent les hallucinations?

Intravenous levodopa in hallucinating Parkinson's disease patients: High-dose challenge does not precipitate hallucinations

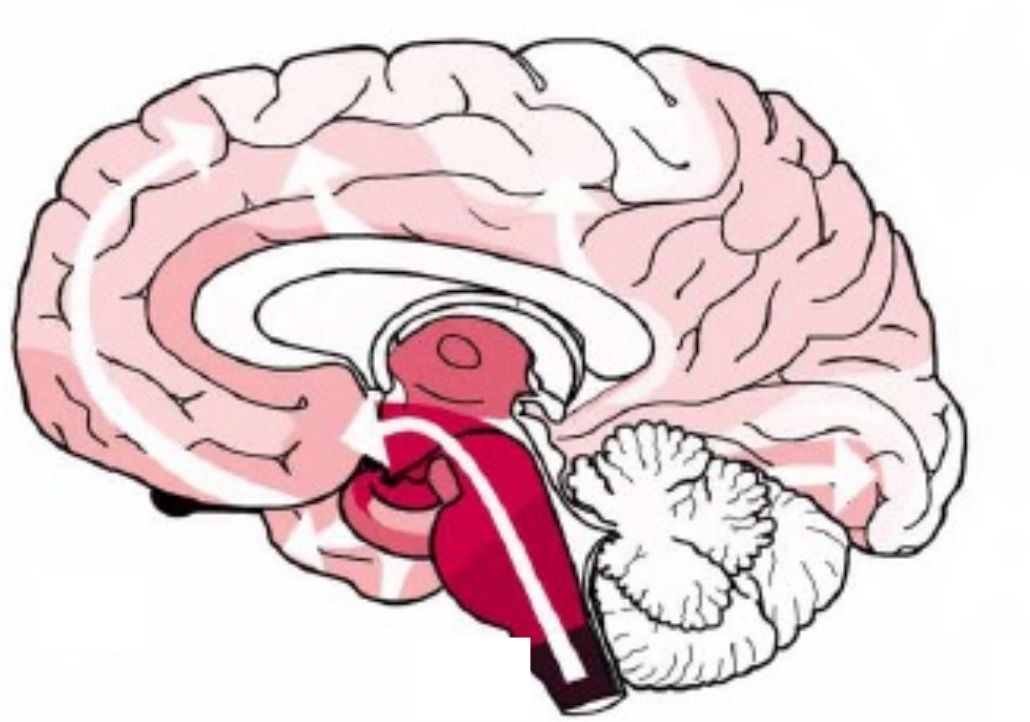
Article abstract—In five nondemented Parkinson's disease patients with daily visual hallucinations, we tested whether high-dose IV levodopa (LD) infusions precipitated hallucinations. Two infusion paradigms were studied, each with 1.5-mg/kg hourly dose for 4 hours—steady infusion and pulse infusion of the full hour dose over 5 minutes each hour. In both protocols, plasma LD levels changed significantly during the infusion protocol. The cumulative area under the curve was equivalent for the two infusions. All patients remained alert, and none developed visual hallucinations. The two patients with peak-dose dyskinesias on oral LD developed prominent dyskinesias during the infusion. Visual hallucinations do not relate simply to high levels of LD or to sudden changes in plasma levels.

NEUROLOGY 1998;50:515–517

C.G. Goetz, MD; E.J. Pappert, MD; L.M. Blasucci, RN; G.T. Stebbins, PhD; Z.D. Ling, PhD; M.V. Nora, PhD; and P.M. Carvey, PhD

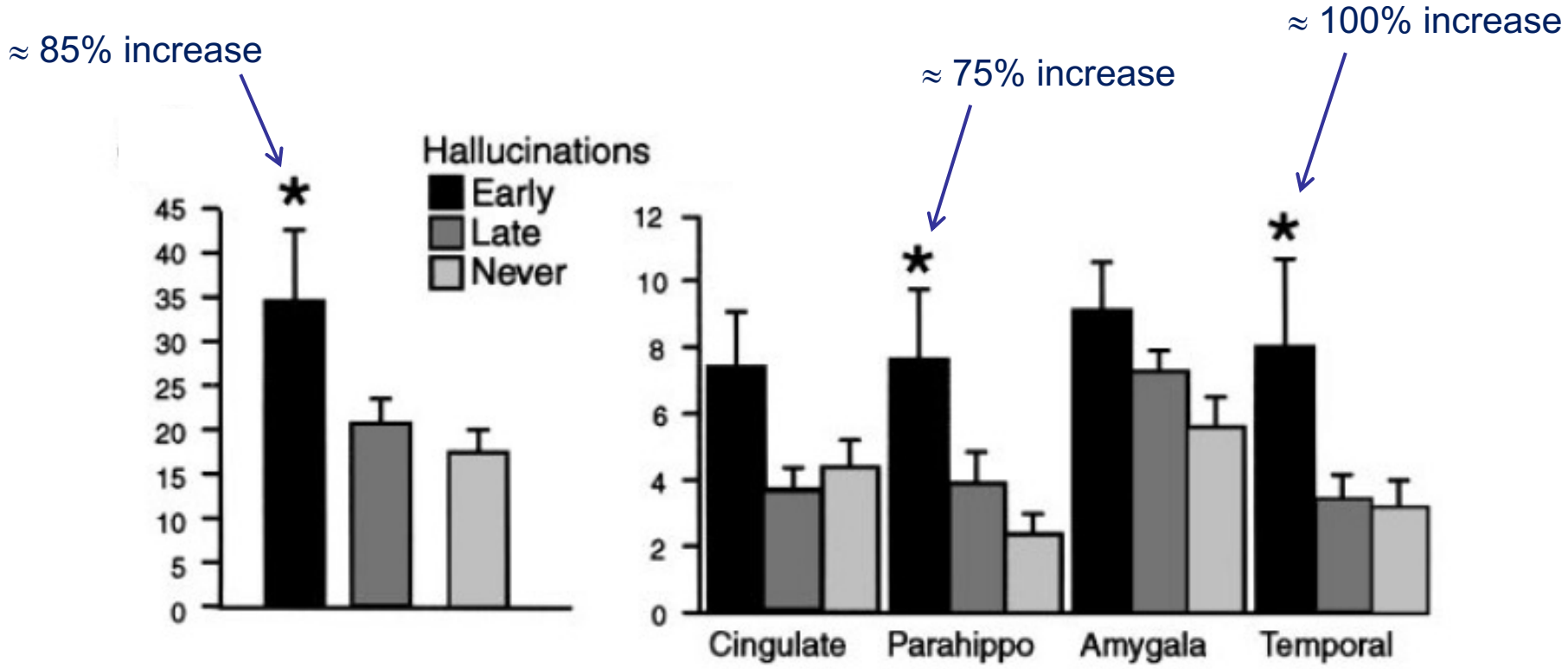
Goetz *et al*. Neurology 1998

Qu’est-ce qui cause les hallucinations?



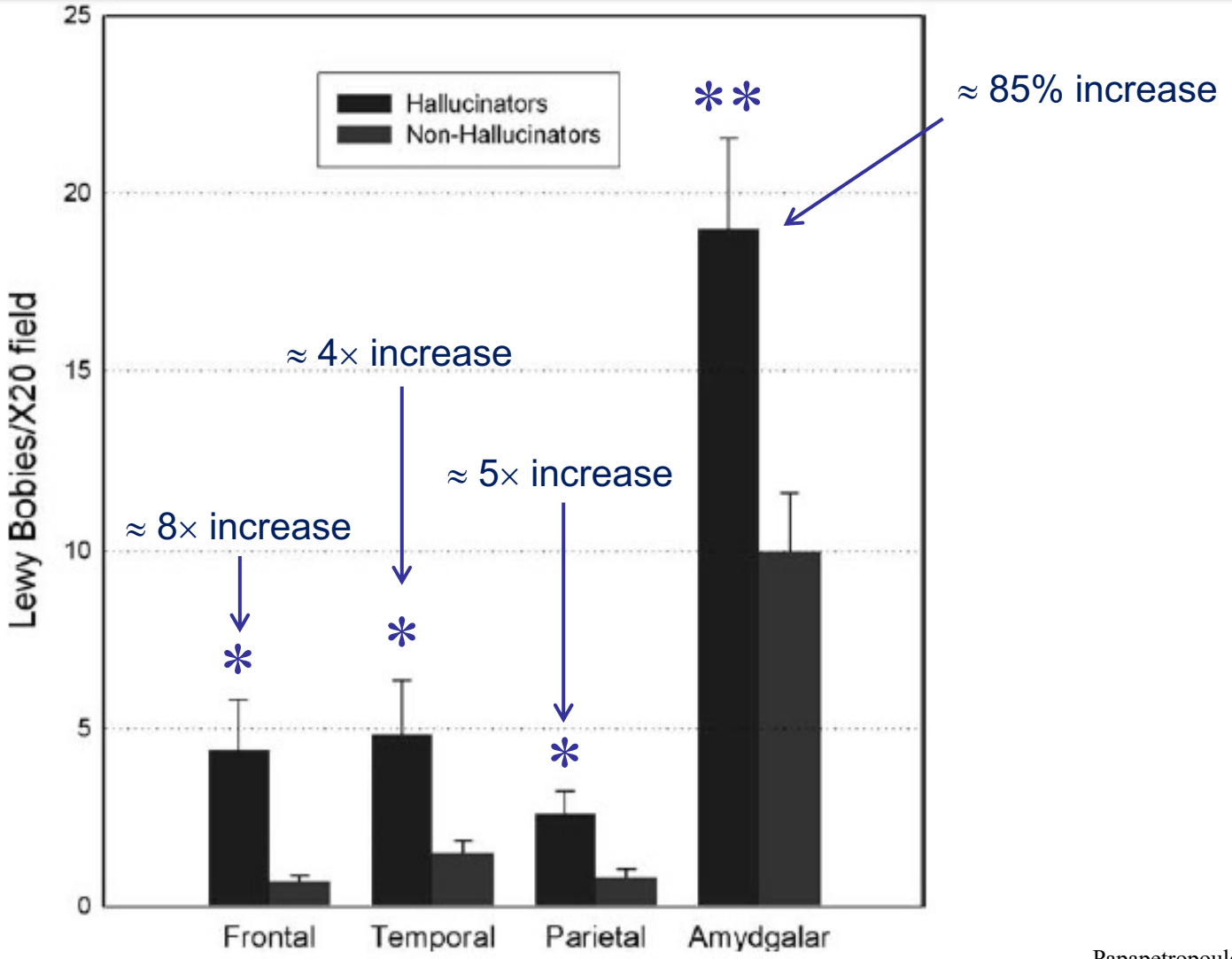
Braak *et al*. Neurobiol Aging 2003

Qu’est-ce qui cause les hallucinations?



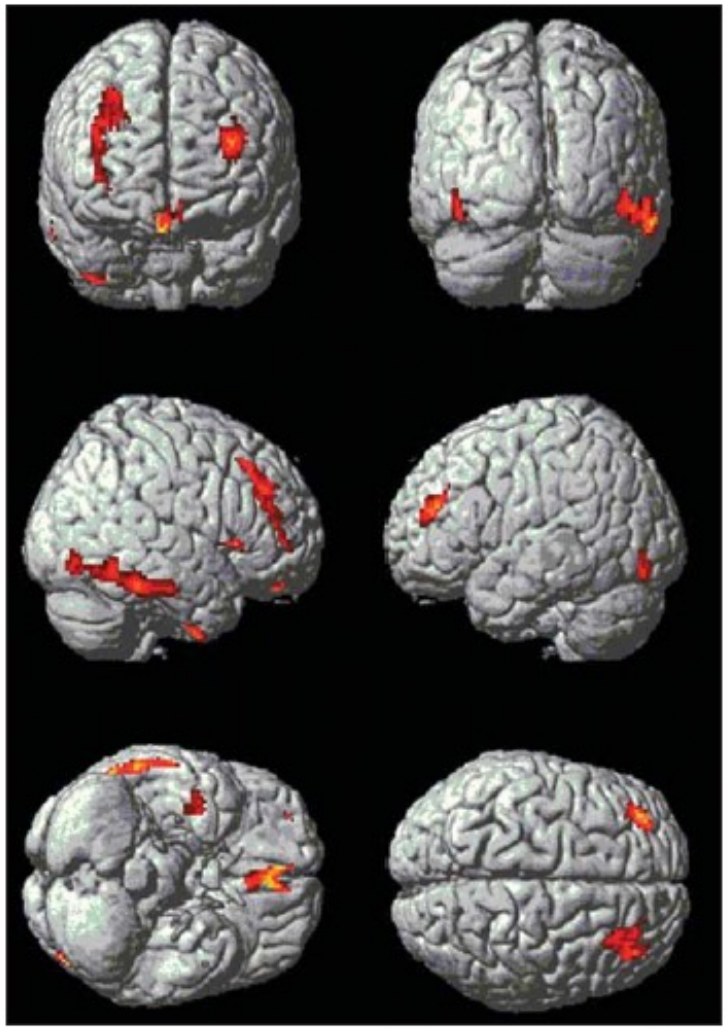
Harding *et al*. Brain 2002

Qu’est-ce qui cause les hallucinations?



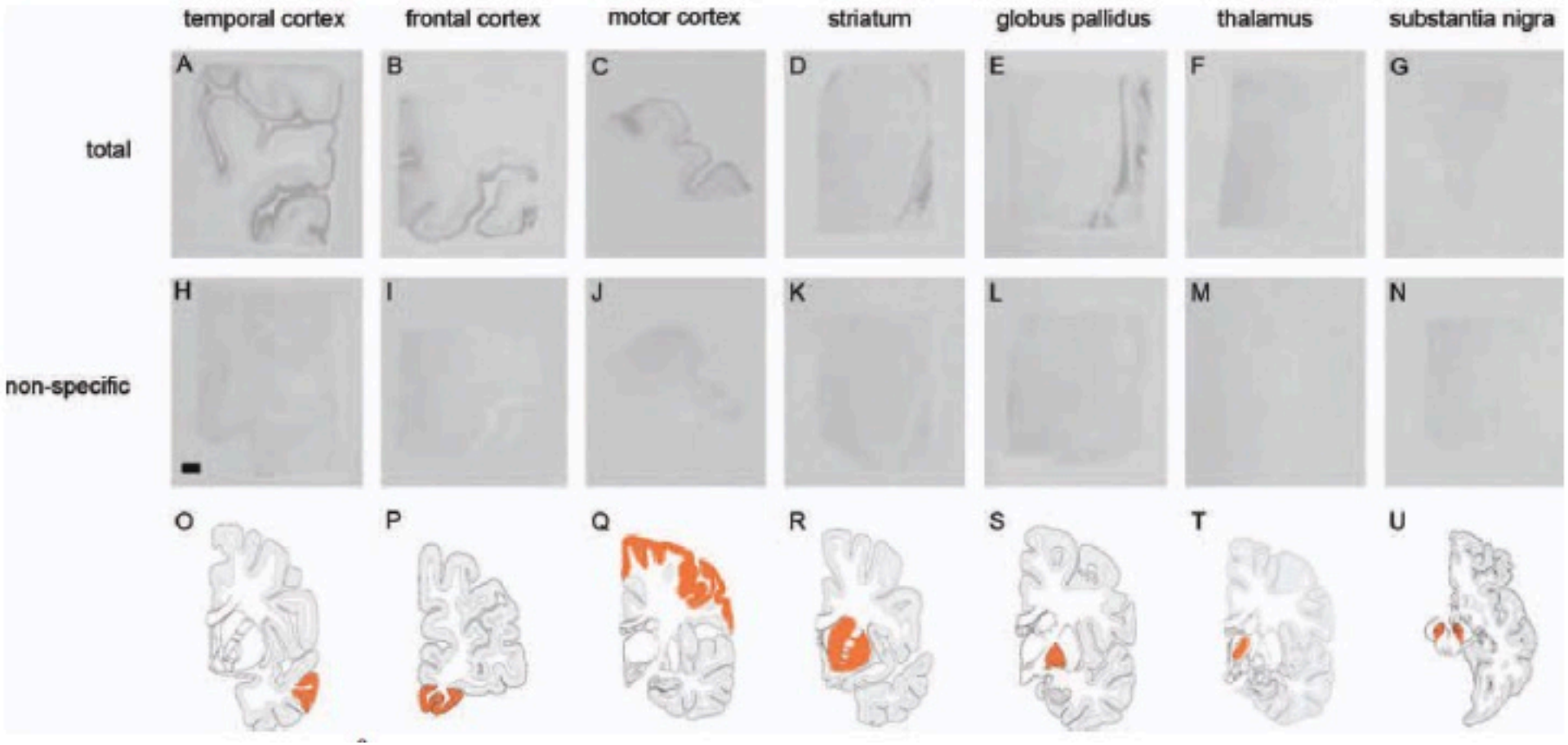
Papapetropoulos *et al*. Parkinsonism Relat Disord 2006

Qu’est-ce qui cause les hallucinations?



Ballanger *et al*. Arch Neurol 2010

Qu’est-ce qui cause les hallucinations?



Huot *et al*. Mov Disord 2012

Y a-t-il des traitements pour les hallucinations?

- Oui!

- Quetiapine (Seroquel®)
- Clozapine (Clozaril®)
- Pimavanserin (Nuplazid®)
- Rivastigmine (Exelon®)

- Les autres médicaments… prudence

Traitements pour les hallucinations dans la maladie de Parkinson

MDS COMMISSIONED REVIEW

CME

Update on Treatments for Nonmotor Symptoms of Parkinson's Disease—An Evidence-Based Medicine Review

Klaus Seppi, MD,[1*] K. Ray Chaudhuri, MD,[2] Miguel Coelho, MD,[3] Susan H. Fox, MRCP (UK), PhD,[4] Regina Katzenschlager, MD,[5] Santiago Perez Lloret, MD,[6] Daniel Weintraub, MD,[7,8] Cristina Sampaio, MD, PhD,[9,10]

TABLE 6. Interventions to treat psychosis in PD

Drug	Efficacy	Safety[a]	Practice implications
Clozapine	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
Olanzapine	*Not efficacious*	Unacceptable risk	*Not useful*
Quetiapine	Insufficient evidence	Acceptable risk without specialized monitoring	*Possibly useful*[b]
Pimavanserin	*Efficacious*	*Acceptable risk without specialized monitoring*[c]	*Clinically useful*

Seppi *et al*. Mov Disord 2019

Quetiapine

The *Movement* Disorder Society Evidence-Based Medicine Review Update: Treatments for the Non-Motor Symptoms of Parkinson's Disease

Klaus Seppi, MD,[1*] Daniel Weintraub, MD,[2] Miguel Coelho, MD,[3] Santiago Perez-Lloret, MD, PhD,[4] Susan H. Fox, MRCP (UK), PhD,[5] Regina Katzenschlager, MD,[6] Eva-Maria Hametner, MD,[1] Werner Poewe, MD,[1] Olivier Rascol, MD, PhD,[4] Christopher G. Goetz, MD,[7] and Cristina Sampaio, MD, PhD[8*]

®

Quetiapine (Six New Studies,[53,54,60–63] *Conclusion: Insufficient Evidence)*. Six studies[53,54,60–63] using quetiapine for the treatment of psychosis in PD were published since the original MDS review in 2002. Two of the studies were clozapine-controlled randomized trials, which were rater-blinded only and 4 of the studies

Safety Conclusion Related to Quetiapine (Conclusion: Acceptable Risk Without Specialized Monitoring). There were no new safety concerns identified in the above

Seppi *et al*. Mov Disord 2011

Clozapine

Clinical Trial > N Engl J Med. 1999 Mar 11;340(10):757-63.

doi: 10.1056/NEJM199903113401003.

Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease

Parkinson Study Group

PMID: 10072410 DOI: 10.1056/NEJM199903113401003

Free article

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NEJM FREE FULL TEXT

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Clinical Trial > Lancet. 1999 Jun 12;353(9169):2041-2.

Clozapine in drug-induced psychosis in Parkinson's disease. The French Clozapine Parkinson Study Group

No authors listed

PMID: 10376627

FULL TEXT LINKS

THE LANCET FULL-TEXT ARTICLE

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Pimavanserin

Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial

Jeffrey Cummings, Stuart Isaacson, Roger Mills, Hilde Williams, Kathy Chi-Burris, Anne Corbett, Rohit Dhall, Clive Ballard

Summary

Background Parkinson's disease psychosis, which includes hallucinations and delusions, is frequent and debilitating in people with Parkinson's disease. We aimed to assess safety and efficacy of pimavanserin, a selective serotonin 5-HT2A inverse agonist, in this population.

Methods In our 6 week, randomised, double-blind, placebo-controlled study, we enrolled adults (aged ≥40 years) with Parkinson's disease psychosis. Antipsychotic treatments were not permitted during the study, but controlled antiparkinsonian medication or deep brain stimulation was allowed. Eligible participants entered a 2 week non-pharmacological lead-in phase to limit the placebo response, after which they were randomly allocated (1:1) to receive pimavanserin 40 mg per day or matched placebo. The primary outcome was antipsychotic benefit as assessed by central, independent raters with the Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD) in all patients who received at least one dose of study drug and had a SAPS assessment at baseline and at least one follow-up. We assessed safety and tolerability in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01174004.

Findings Between Aug 11, 2010, and Aug 29, 2012, we randomly allocated 199 patients to treatment groups. For 90 recipients of placebo and 95 recipients of pimavanserin included in the primary analysis, pimavanserin was associated with a −5·79 decrease in SAPS-PD scores compared with −2·73 for placebo (difference −3·06, 95% CI −4·91 to −1·20; p=0·001; Cohen's *d* 0·50). Ten patients in the pimavanserin group discontinued because of an adverse event (four due to psychotic disorder or hallucination within 10 days of start of the study drug) compared with two in the placebo group. Overall, pimavanserin was well tolerated with no significant safety concerns or worsening of motor function.

Interpretation Pimavanserin may benefit patients with Parkinson's disease psychosis for whom few other treatment options exist. The trial design used in this study to manage placebo response could have applicability to other studies in neuropsychiatric disease.

Cummings *et al*. Lancet Neurol 2013

Pimavanserin

FDA NEWS RELEASE

FDA approves first drug to treat hallucinations and delusions associated with Parkinson's disease

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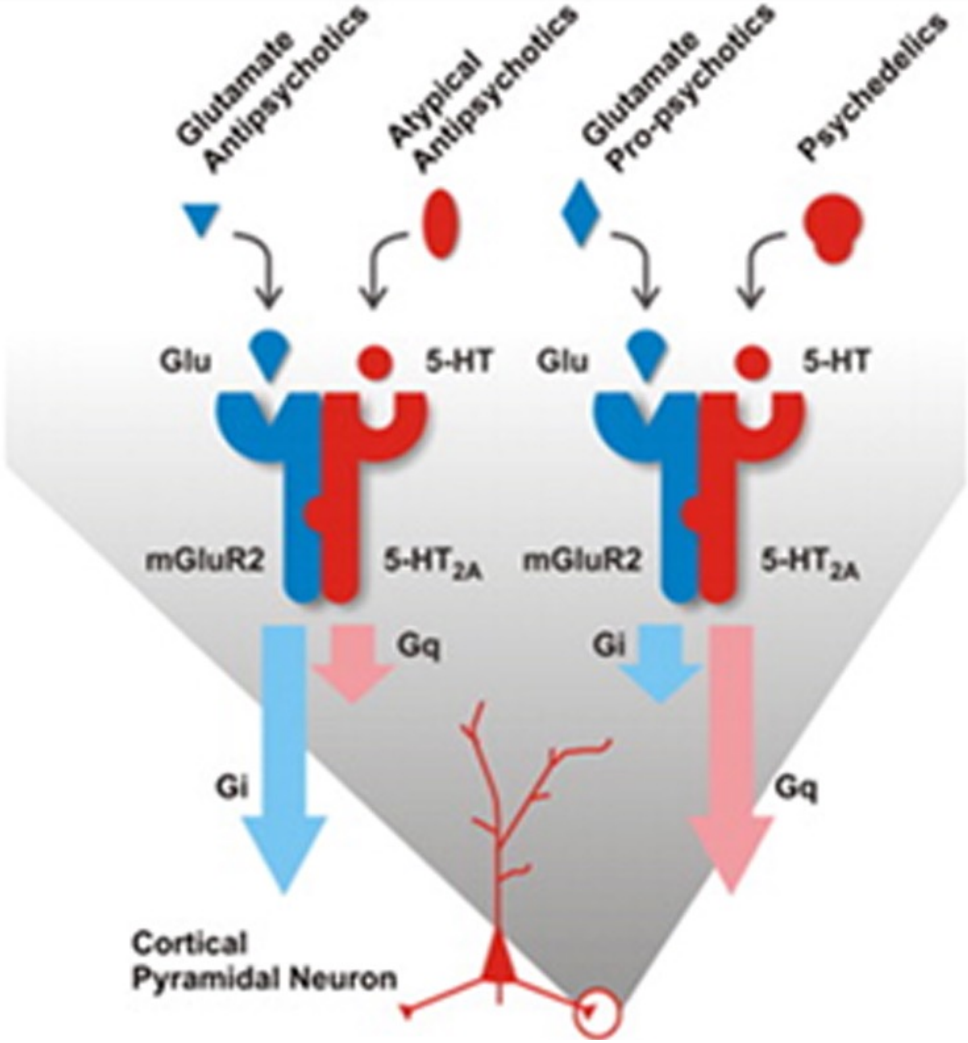
For Immediate Release: April 29, 2016

The U.S. Food and Drug Administration today approved Nuplazid (pimavanserin) tablets, the first drug approved to treat hallucinations and delusions associated with psychosis experienced by some people with Parkinson's disease.

https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-hallucinations-and-delusions-associated-parkinsons-disease

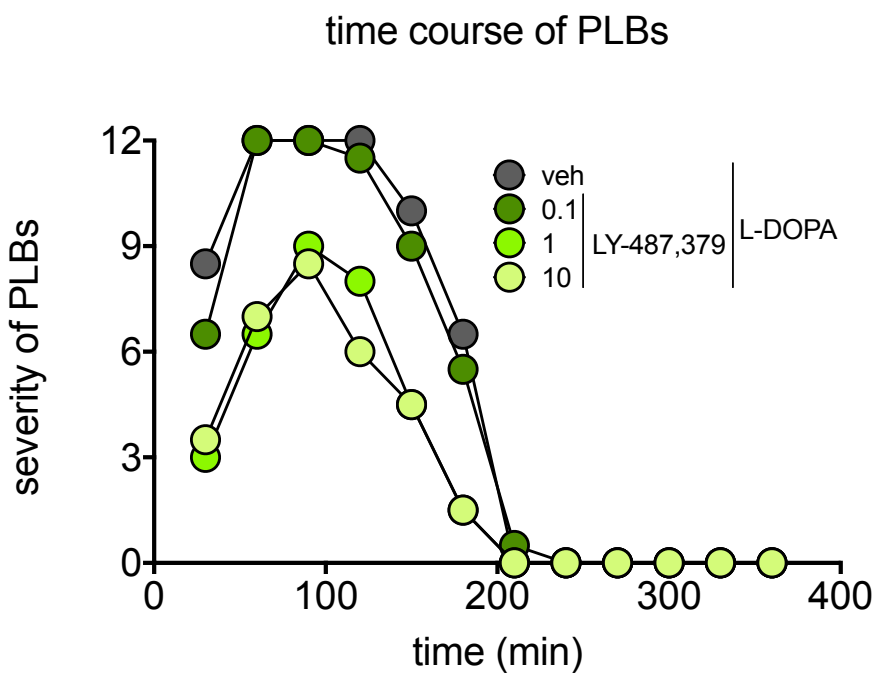
Les récepteurs $mGlu_2$, une nouvelle cible thérapeutique pour la maladie de Parkinson

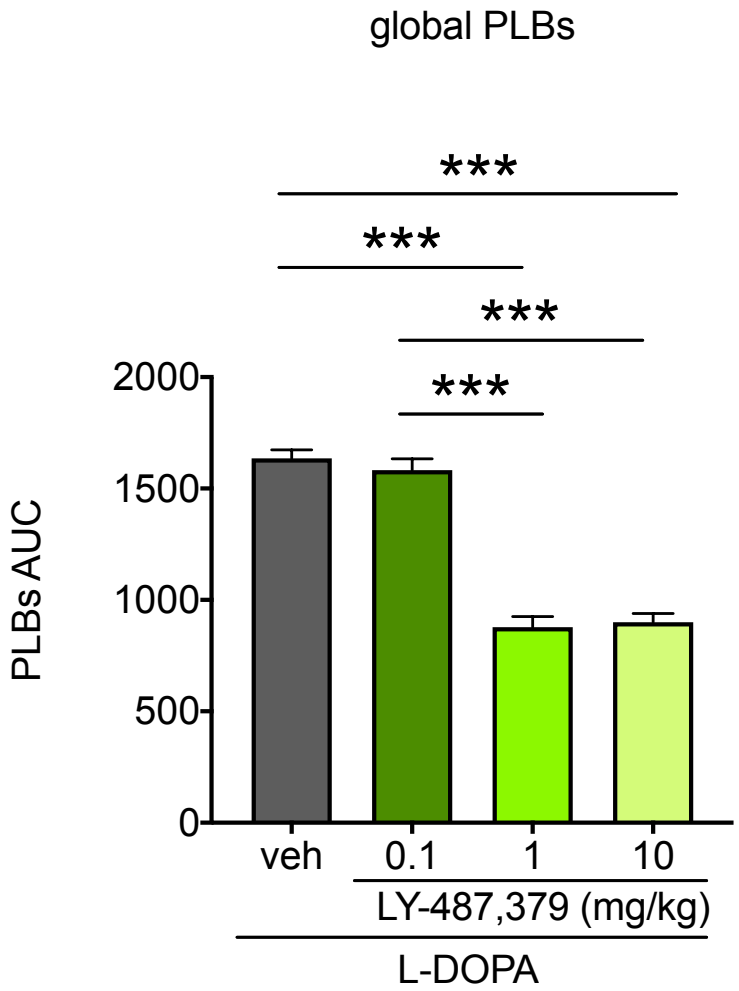
Activation des récepteurs $mGlu_2$ dans la psychose



Fribourg *et al*. Cell 2011

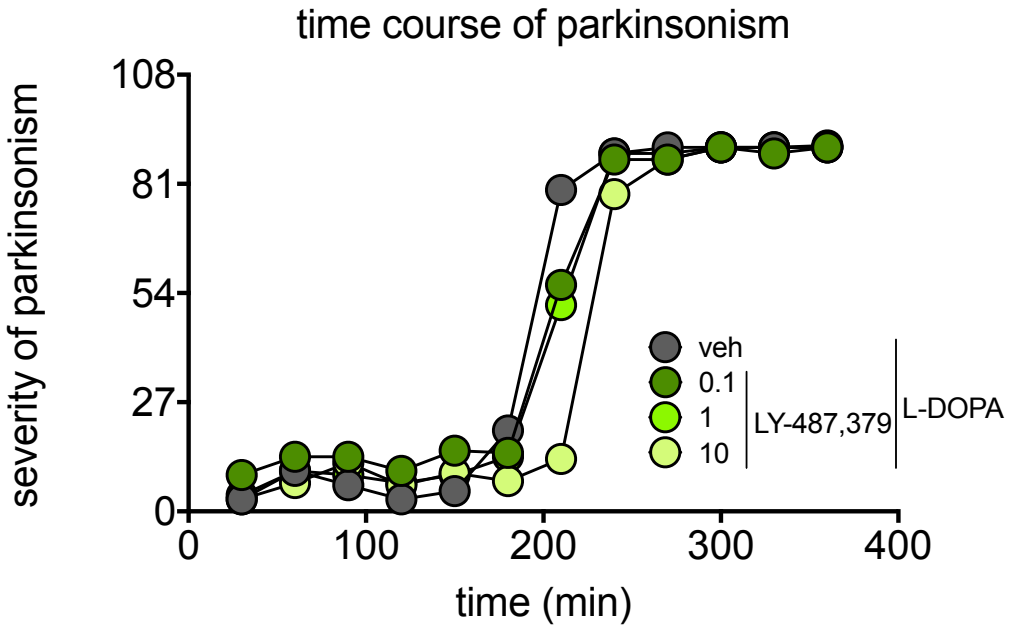
Effet du modulateur allostérique positif des récepteurs $mGlu_2$ LY-487,379 sur la psychose parkinsonienne

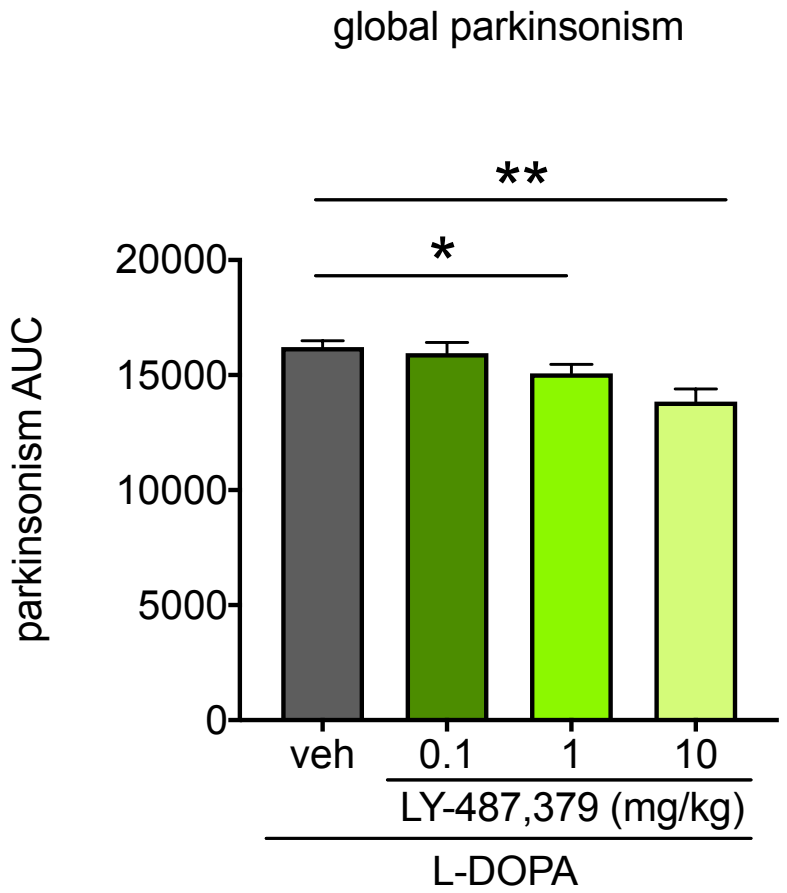




Sid-Otmane *et al*. Eur J Pharmacol 2020

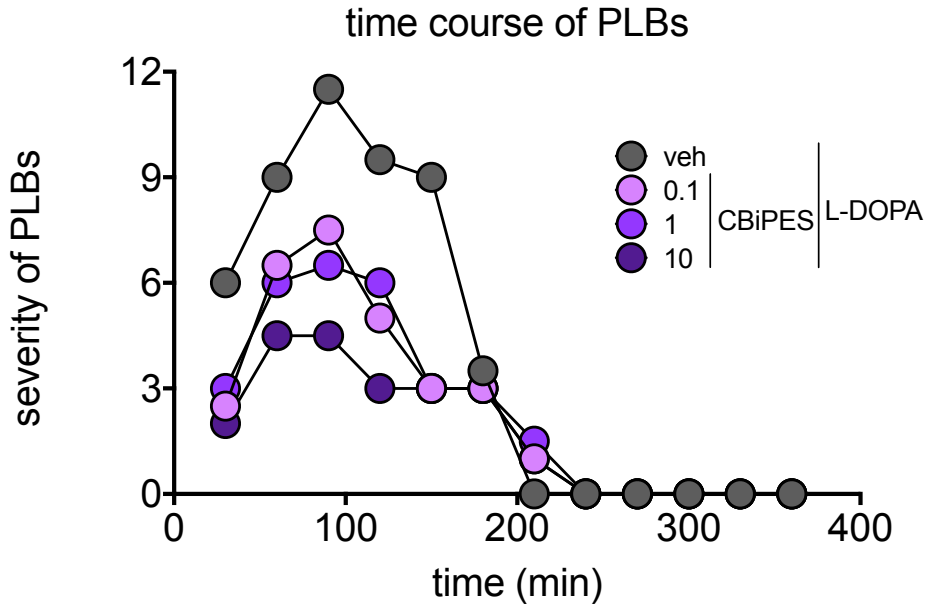
Effet du modulateur allostérique positif des récepteurs $mGlu_2$ LY-487,379 sur le parkinsonisme

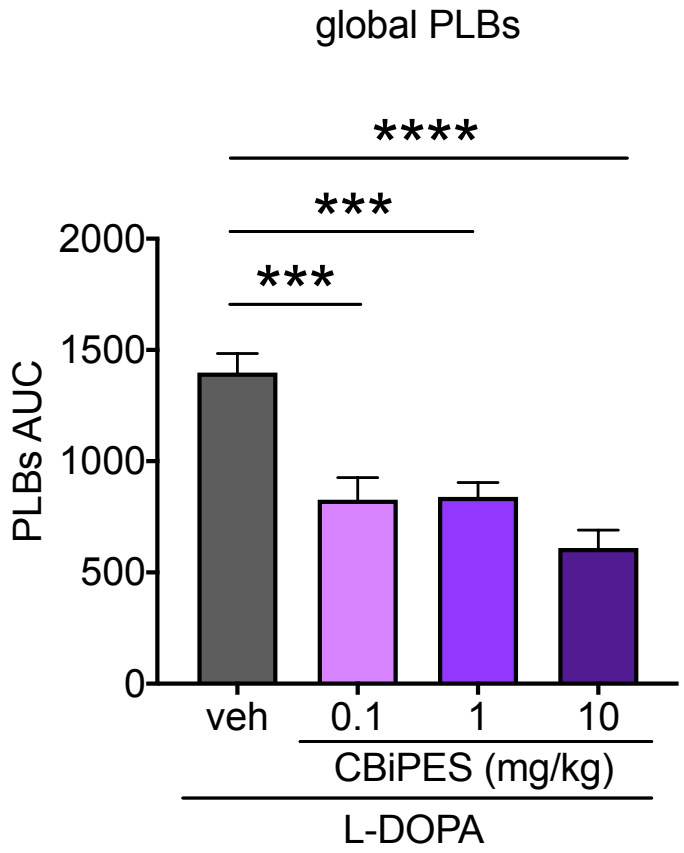




Sid-Otmane *et al*. Eur J Pharmacol 2020

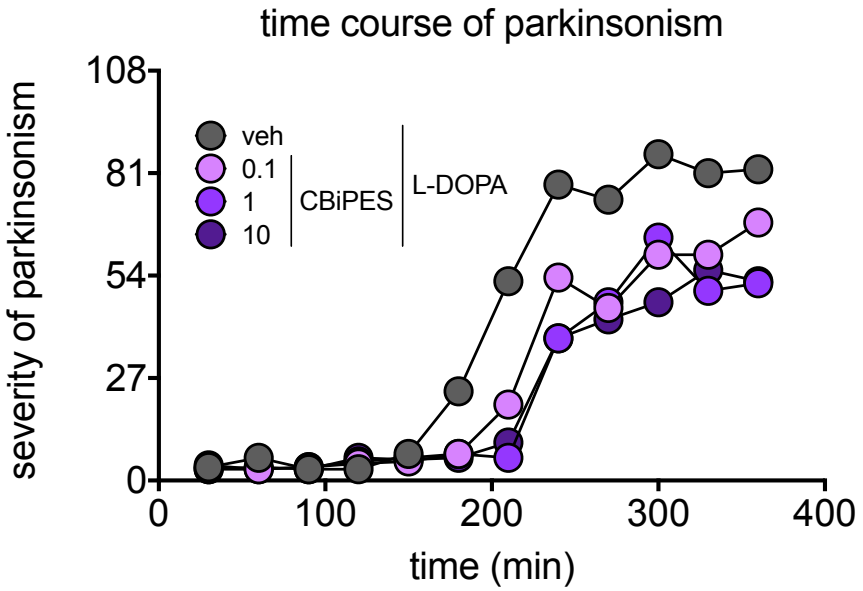
Effet du modulateur allostérique positif des récepteurs $mGlu_2$ CBiPES sur la psychose parkinsonienne

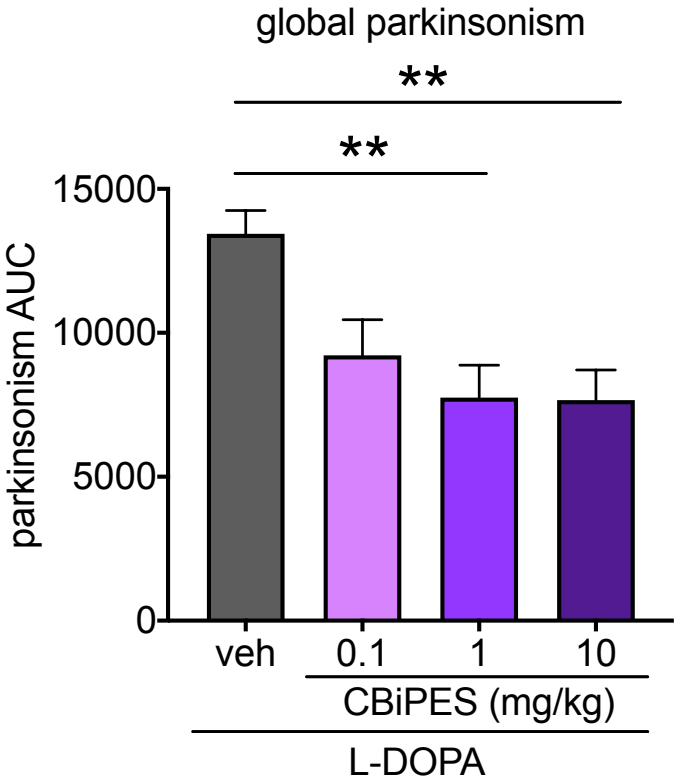




Frouni *et al*. J Neural Transm 2021

Effet du modulateur allostérique positif des récepteurs $mGlu_2$ CBiPES sur le parkinsonisme





Frouni *et al*. J Neural Transm 2021

Résumé

- Les hallucinations visuelles sont fréquentes
- Les hallucinations visuelles surviennent surtout dans les stades avancés de la maladie
- Les médicaments anti-parkinsoniens ont un rôle mineur tout au plus dans les hallucinations visuelles
- Il existe des médicaments pour traiter les hallucinations visuelles, mais leur efficacité est limitée ou ils peuvent produire des effets secondaires
- L'activation des récepteurs $mGlu_2$ représente une nouvelle avenue thérapeutique pour le traitement de la psychose parkinsonienne