

Agitation nocturne et iatrogénie en psychiatrie

Dr Régis LOPEZ, MD, PhD

*Centre national de référence Narcolepsie /
hypersomnie idiopathique*

Unité des troubles du sommeil

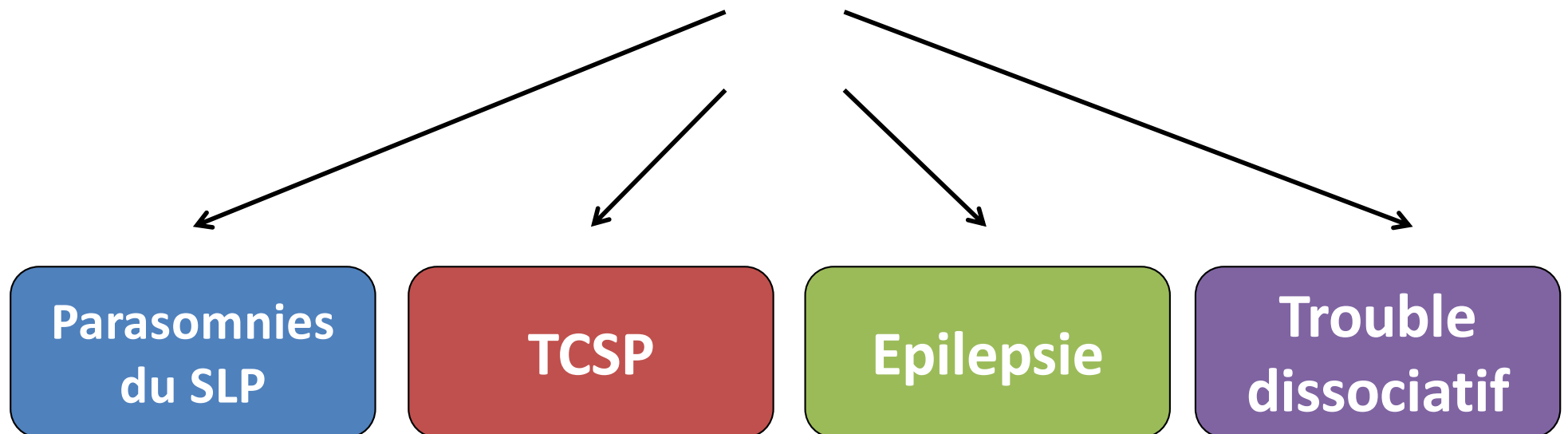


Pas de conflits d'intérêt



AGITATION
au cours du sommeil

Ce n'est pas
Eveil anxieux post-cauchemar
Attaques de panique nocturne



Somnambulisme



Terreur nocturne



Eveil confusionnel



PARASOMNIES DU SOMMEIL LENT PROFOND

Terreur nocturne

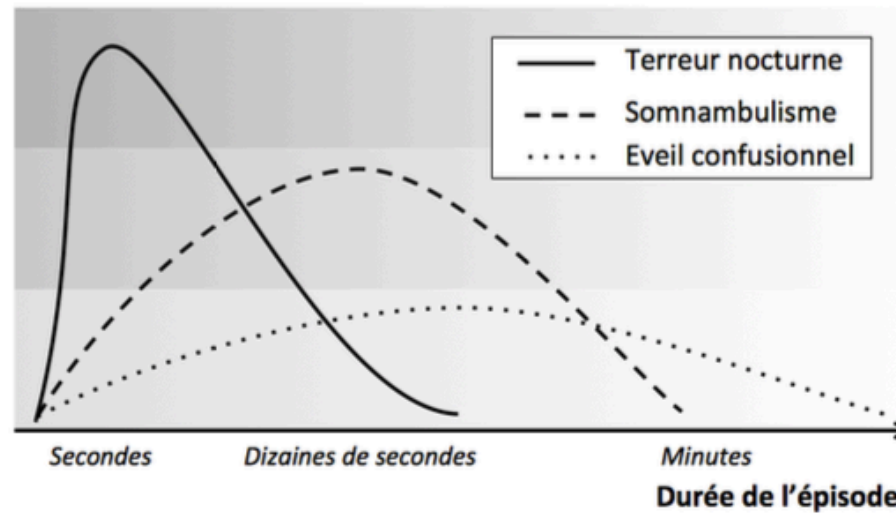
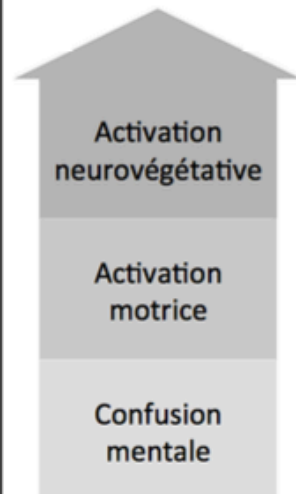
Somnambulisme

Eveil confusionnel

Composante
neurovégétative +++

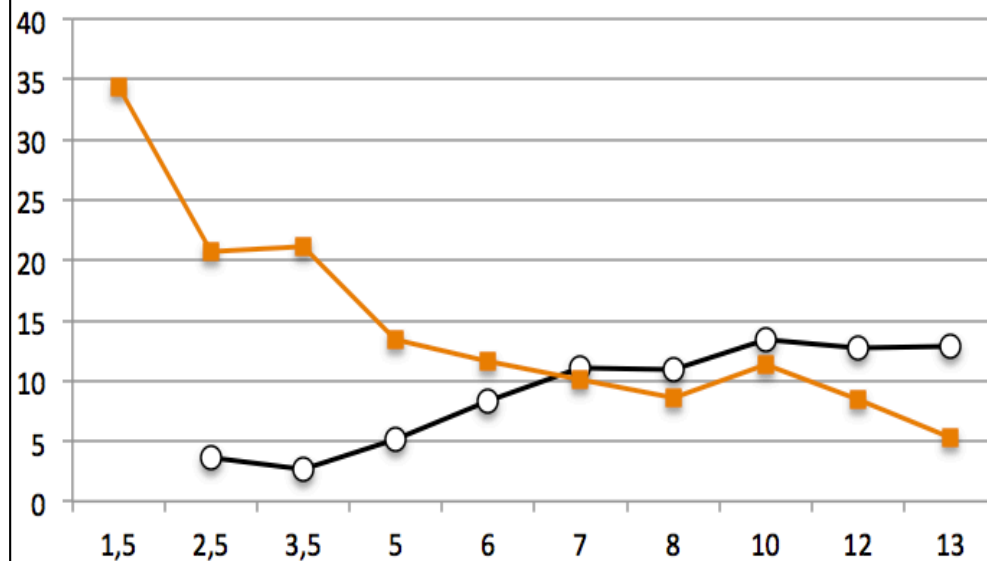
Composante motrice +++

Confusion +++

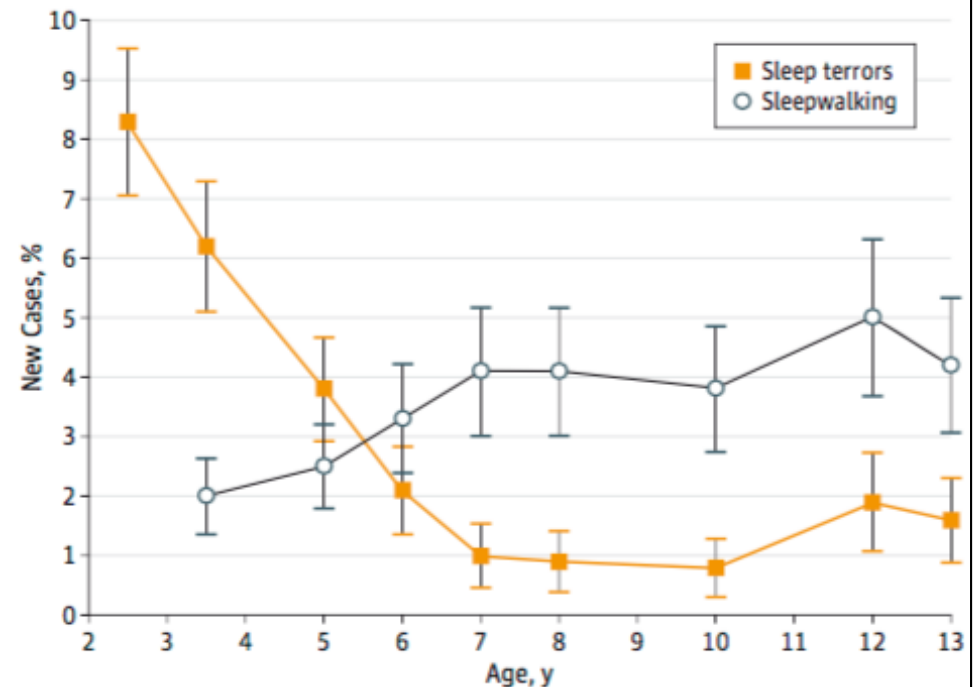


Diagnostic clinique
ICSD-3 / DSM-5 / ICD-10

Prévalence



Incidence



Sex-ratio 1:1

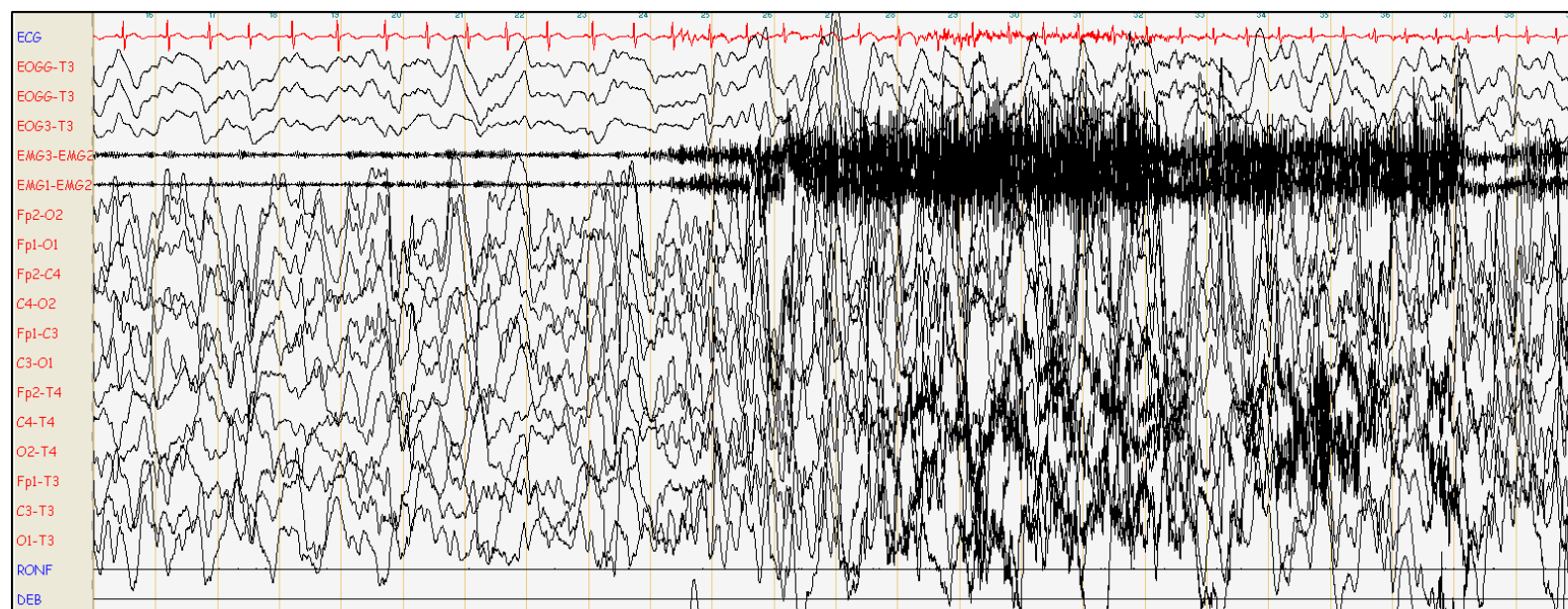
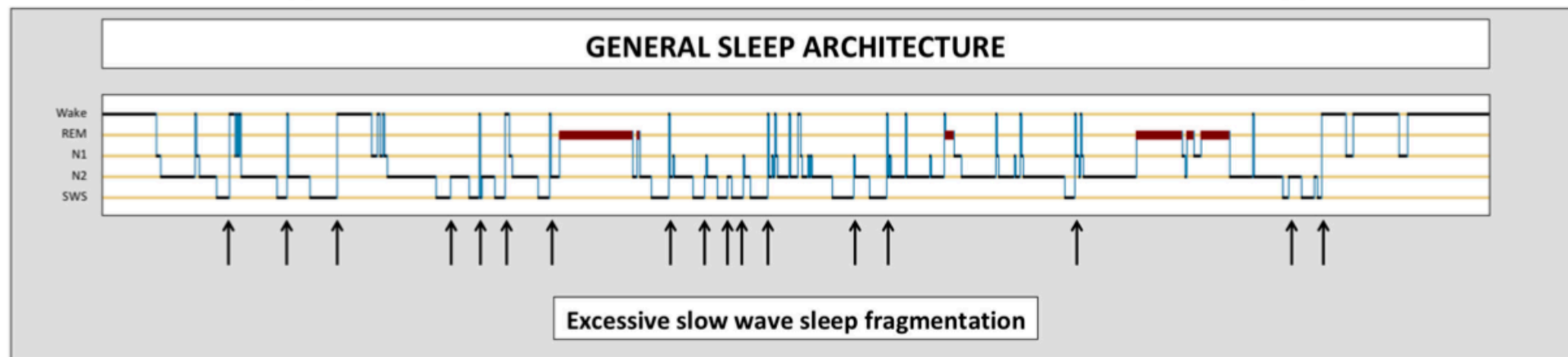
Current sleepwalking (children) : **5.0%** (95% CI 3.8 – 6.5)
(31 studies)

Current sleepwalking (adults) : **1.5%** (95%CI 1.0 – 2.3)
(9 studies)

Lifetime sleepwalking : **6.9%** (95%CI 4.6 – 10.3)
(20 studies)

Petit et al. 2015

Stallman et al. 2016



Episode parasomniaque

Retentissement

Parasomnies du SLP

Psychopathologie

Fréquence des troubles psychiatriques très variable

(10% - 85%)

Kales et al. 1980

Schenck et al. 1989, 1996

Lopez et al. 2013

Ohayon et al. 2012, 2014

Somnolence / fatigue

Fréquence de la plainte de somnolence très variable

(4% - 46.5%)

Fatigue **75%**

Guilleminault et al. 2005

Oudiette et al. 2009

Lopez et al. 2013, 2014

Nombreux rapports de cas

Fonctionnement cognitif

Peu d'arguments pour une altération du fonctionnement cognitif en condition basale, mais **sensibilité** à la **privation de sommeil**

Uguccioni et al. 2015

Labelle et al. 2015

Plaintes somatiques / douleurs

Plus d'hospitalisations, « physical illness »
Forte association avec la **migraine**

Ohayon et al. 1999, 2012, 2014

Casez et al. 2005

Miller et al. 2003

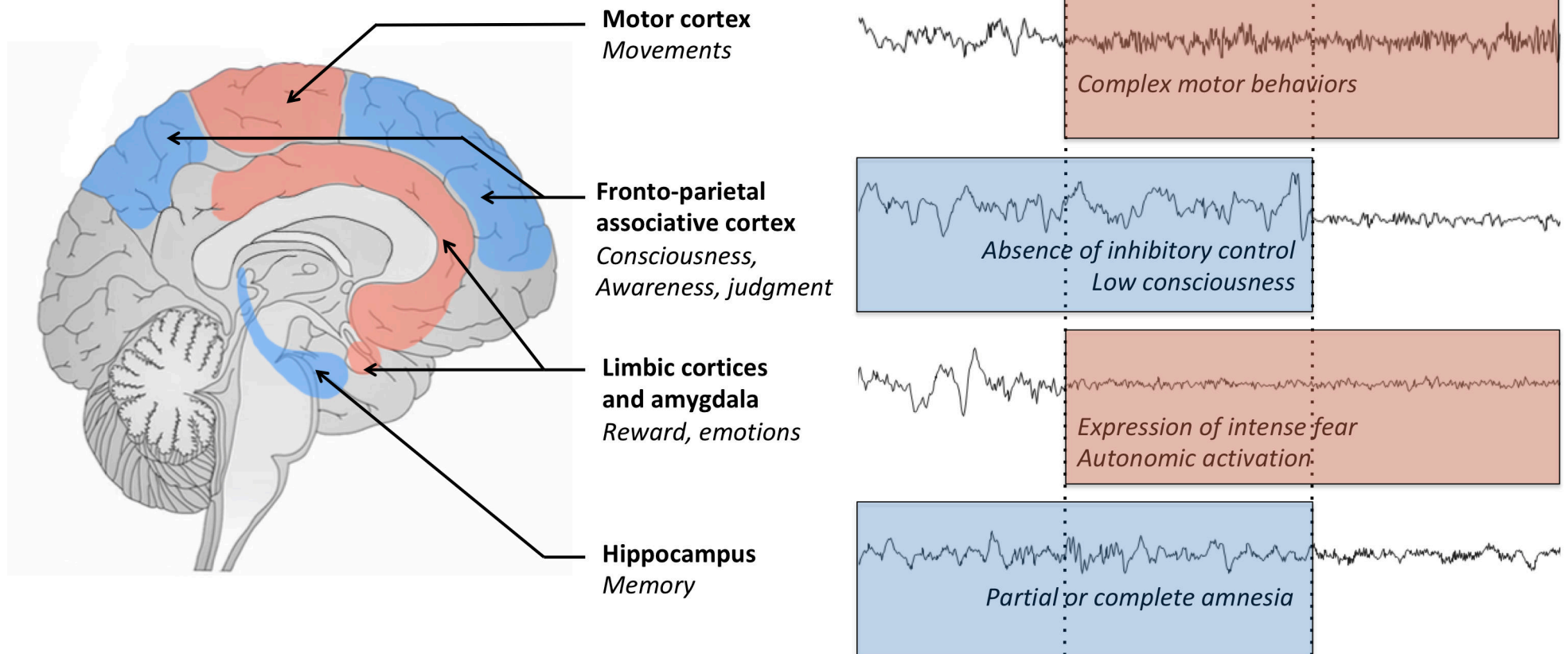
Lopez et al. 2015

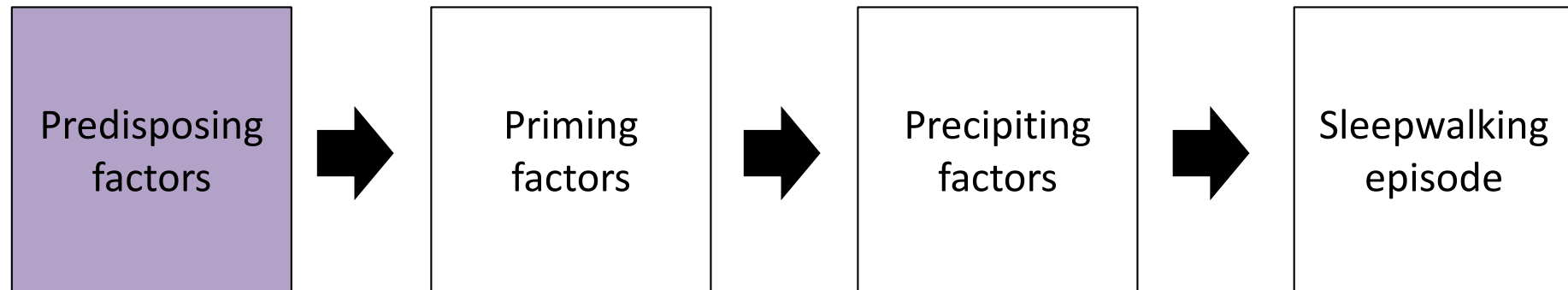
Qualité de vie

Lopez et al. 2013

Modèle de l'éveil dissocié

FIGURE 3: Sleep-wake dissociation in disorders of arousal





Prédisposition génétique

Fréquence élevée de parasomnies chez les apparentés

Chez l'enfant :

1 parent atteint : risque X3

2 parents atteints : risque X7

Cohortes de jumeaux :

Enfants MZ = 1,5 X DZ

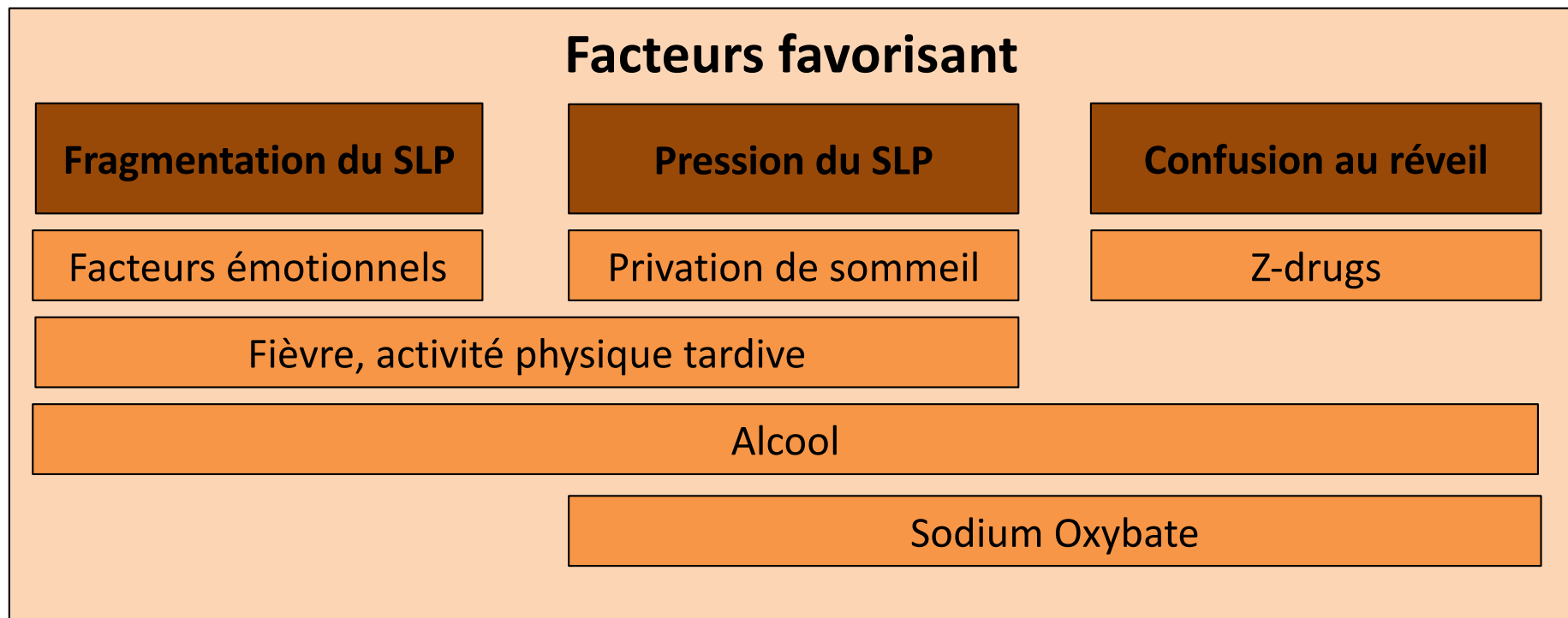
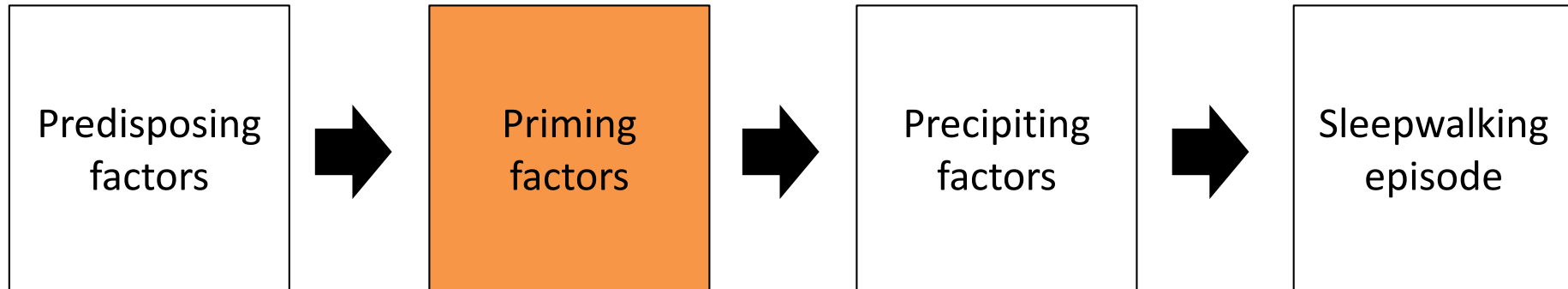
Adultes MZ = 5 X DZ

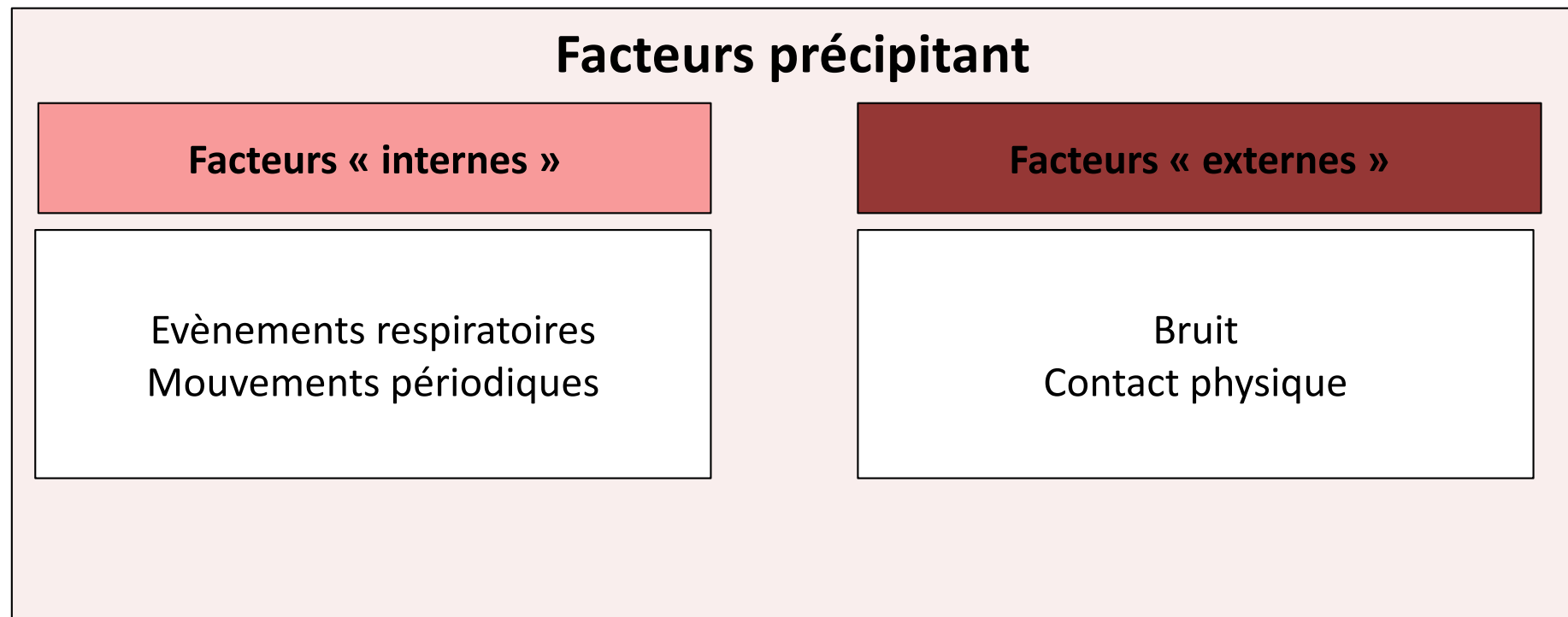
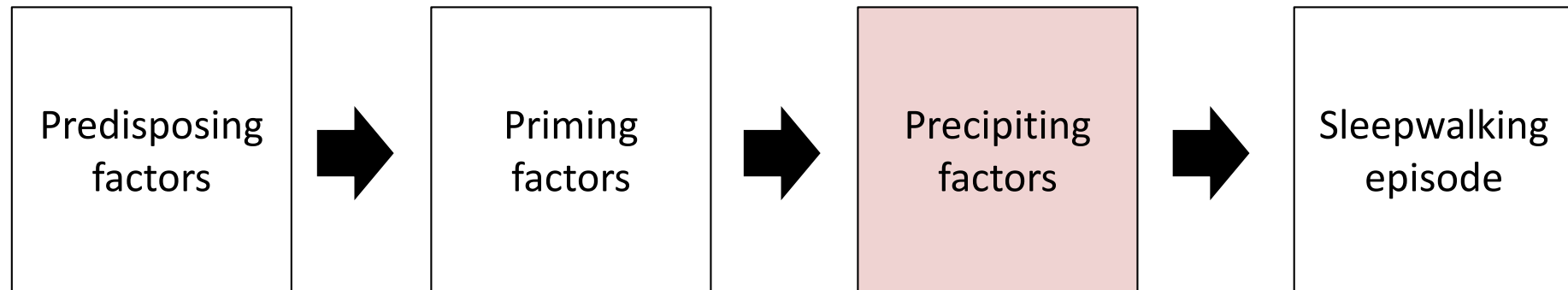
Petit et al. 2015

Pressman 2007

Kales et al. 1980

Hublin et al. 1997





Parasomnies du SLP et iatrogénie

Characteristics of included studies.

Class of drugs	Drug names	No. of studies	Citation	Years published	Study design	N	Sex ^a	Age (y) ^a
Benzodiazepine receptor agonists and other GABA modulators	Zolpidem	24	[43]	1988	Clinical trial	1 (1.04%)	ns	ns
			[52]	1988	Case report	1	M = 1	46
			[53]	1994	Case report	1	M = 1	20
			[42] ^b	1995	Clinical trial	5 (0.25%)	ns	ns
			[55]	1999	Case report	1	M = 1	46
			[50] ^b	2003	Case report	1	M = 1	47
			[46] ^b	2003	Case report	1	M = 1	66
			[54]	2004	Case report	1	M = 1	47
			[59]	2005	Case report	1	F = 1	13
			[49] ^b	2005	Case report	1	M = 1	19
			[45]	2005	Case report	1	M = 1	ns
			[61] ^b	2008	Case report	1	F = 1	51
			[44]	2009	Clinical trial	3 (2.2%)	ns	ns
			[62] ^b	2009	Case report	1	F = 1	51
			[58] ^b	2009	Case report	1	M = 1	79
			[48]	2009	Case report	1	F = 1	44
			[41] ^b	2009	Survey	13	M = 6	25–57
			[40] ^b	2010	Survey	6	ns	ns
			[60] ^b	2010	Case report	2	F = 2	15, 16
			[56]	2011	Case report	1	M = 1	49
			[51] ^b	2011	Case report	8	M = 4	43–65
							F = 4	28–65
			[57] ^b	2015	Case report	1	M = 1	46
			[47] ^b	2015	Case report	1	M = 1	60s
			[63]	2015	Case report	2	M = 1	31
	Zaleplon	2	[65]	2004	Case report	1	M = 1	14
	Zopiclone	1	[64]	2014	Case report	1	M = 1	43
			[66] ^b	2009	Case report	1	F = 1	55

						Parasomnies du SLP		
Anticonvulsant	Topiramate	2	[68]	2003	Case report	1	F = 1	35
Sedative hypnotics	Choral hydrate	1	[67]	2012	Case report	2	M = 2	26, 81
	Methaqualone	1	[69]	1956	Case report	2	M = 2	26, 81
	Sodium oxybate	1	[70] ^b	1976	Case report	3	F = 3	29–54
Antidepressants and other serotonergic agents			[72]	2005	Clinical trial	3 (1.22%)	ns	ns
	Tricyclic	1	[73] ^b	2000	Case report	1	F = 1	50
	SSRI	2	[74] ^b	1999	Case report	1	F = 1	34
			[39]	2003	Case report	1	F = 1	61
		1	[75]	1999	Case report	5	M = 5	ns
		1	[74] ^b	1999	Case report	1	F = 1	34
	SNRI	1	[76]	2009	Case report	1	F = 1	40
		1	[77] ^b	2004	Case report	1	F = 1	18
	Atypical	2	[82]	2003	Case report	1	M = 1	33
			[83] ^b	2010	Case report	1	F = 1	63
Other	Lithium	4	[78] ^b	1979	Case report	10	F = 8	15–49
							M = 2	19–28
			[79]	1998	Case report	1	M = 1	52
			[80] ^b	1999	Case reports	27	F = 14	ns
			[81] ^b	2011	Case report	1	F = 1	50
	Atypical antipsychotics	3	[86]	2001	Case report	1	M = 1	63
			[84] ^b	2008	Case report	1	M = 1	52
			[85]	2012	Case report	1	M = 1	42
		3	[87] ^b	2007	Case report	2	M = 2	18–52
			[81] ^b	2011	Case report	2	F = 2	50, 50
Older generation antipsychotics			[88] ^b	2013	Case report	4	F = 2	59–75
							M = 2	37–53
	Chlorprothixene	1	[71] ^b	1979	Case report	1	F = 1	30
	Perphenazine	1	[71] ^b	1979	Case report	2	F = 1	30
	Thioridazine	2	[89]	1978	Case report	1	F = 1	44
β-blockers			[71] ^b	1979	Case report	1	F = 1	49
	Propranolol	3	[92]	1986	Case report	4	F = 4	34–61
			[91]	1987	Case report	3	F = 3	34–61
			[90]	2014	Case report	1	F = 1	34
	Metoprolol	2	[93]	2008	Case report	1	F = 1	66
Others			[94] ^b	2014	Case report	1	M = 1	79
	Varenicline	1	[99]	2015	Case report	5	ns	ns
	Methyphenidate	1	[97]	2014	Case report	1	M = 1	12
	Bromocriptine and lisuride	1	[96] ^b	1986	Case report	1	F = 1	27
	Suvorexant	1	[98]	2014	Case report	1	ns	ns
	Montelukast	1	[100]	2013	Case report	1	F = 1	16
Antibiotic	Ciprofloxacin	1	[95]	1999	Case report	1	F = 1	10

Parasomnies du SLP et Zolpidem

- Etudes systématiques :
 - ***Tsai et al. 2009***
 13 patients / 255 (5,1%) rapportent un somnambulisme ou des troubles comportementaux au cours du sommeil en rapport avec la prise de Zolpidem :
 - 5 utilisent leur téléphone, 3 regardent la télévision, 1 sort de chez lui et 4 divers comportements inappropriés

Table 1 Clinical and demographic characteristic of the enrolled patients

Zolpidem-induced amnesia/ somnambulism	Patients, n (%)	Age, y	Gender, n (%)	Zolpidem dosage, mg/hs	Diagnosis, n
Yes	13 (5.1%)	42.5 ± 17.1	Male, 6 (46.2%) Female, 7 (53.8%)	10.0 ± 6.1	Schizophrenia, 2 Affective disorders, 3 Anxiety disorders, 3 Sleep disorders, 3 Adjustment disorders, 2
None	242 (94.9%)	43.9 ± 15.9	Male, 108 (44.6%) Female, 134 (55.4%)	15.1 ± 6.2	Schizophrenia, 59 Affective disorders, 78 Anxiety disorders, 42 Sleep disorders, 15 Adjustment disorders, 19
P		.776	.820	.057	Others, 29 .986

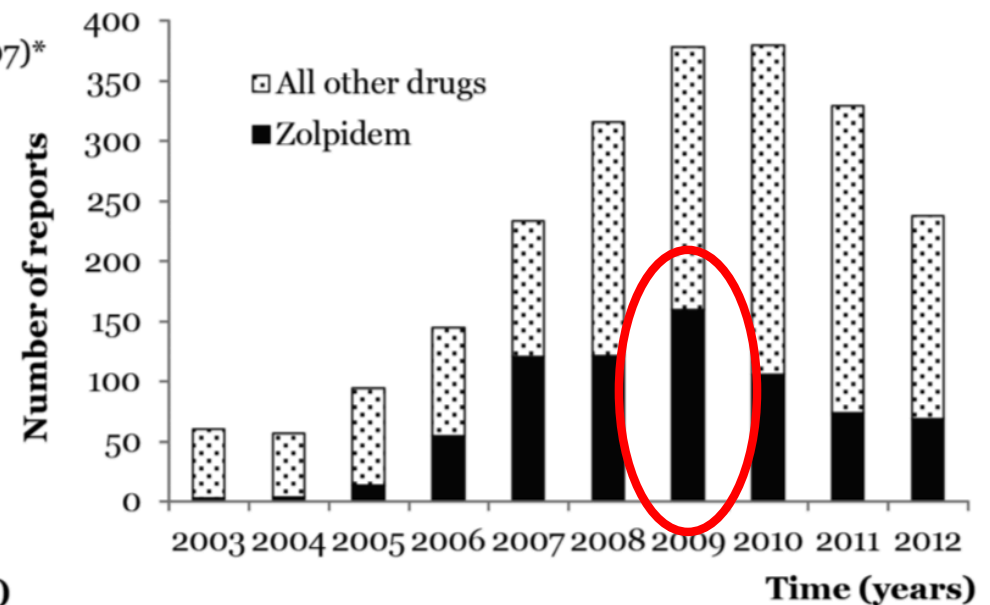
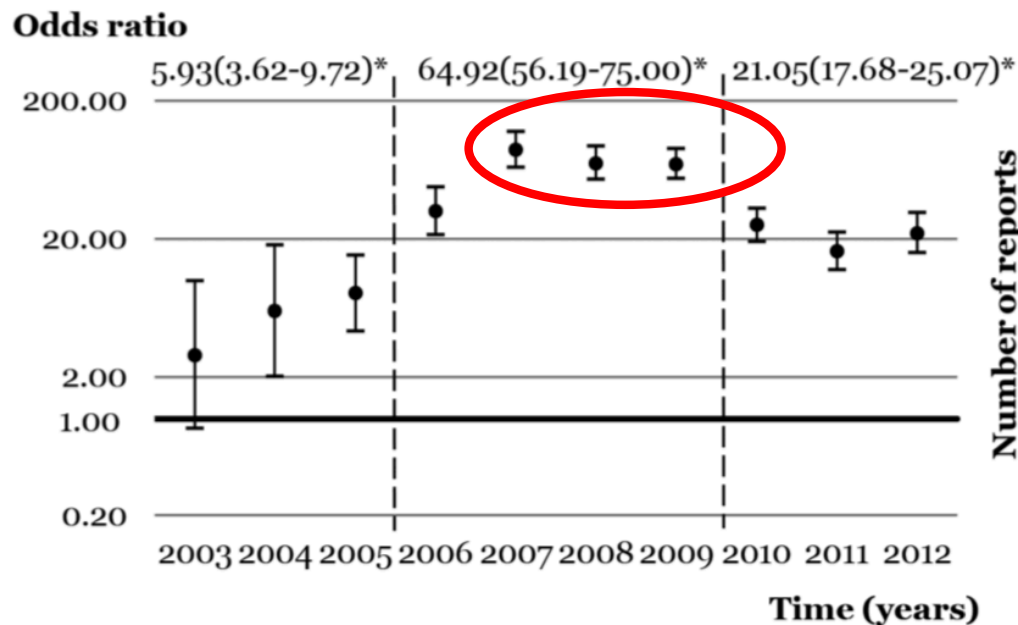
Parasomnies du SLP et Zolpidem

Spontaneous Adverse Event Reports Associated with Zolpidem in the United States 2003–2012

JCSM
Journal of Clinical
Sleep Medicine

Carmen K. Wong, BPharm¹; Nathaniel S. Marshall, PhD^{2,3}; Ronald R. Grunstein, MD²; Samuel S. Ho, BPharm¹; Romano A. Fois, PhD¹; David E. Hibbs, PhD¹; Jane R. Hanrahan, PhD¹; Bandana Saini, PhD^{1,2}

Covariates in Logistic Regression Models	Odds Ratios for Exposure to Zolpidem					
	Parasomnia		Movement-Based Parasomnia		Nonmovement-Based Parasomnia	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Patient demographics	5.78 (5.45–6.14)	< 0.0001*	34.39 (31.39–37.68)	< 0.0001*	2.12 (1.92–2.34)	< 0.0001*
Patient demographics and drug exposures	4.34 (4.05–4.64)	< 0.0001*	35.20 (31.65–39.14)	< 0.0001*	1.28 (1.15–1.42)	< 0.0001*



Parasomnies du SLP et Zolpidem

Summary

- In February 2008 the Therapeutic Goods Administration (TGA) placed a boxed warning on the product information of medicines containing zolpidem. The warning:
 - highlights potentially dangerous sleep-related behaviours that may be linked to zolpidem use
 - advises that zolpidem should not be taken with alcohol, and that caution is needed with concurrent use of other CNS depressants
 - recommends limiting use to a maximum of 4 weeks.
- In postmarketing reports zolpidem has been associated with a variety of bizarre sleep-related events — such as sleepwalking, sleep-eating and sleep-driving — with patients having no subsequent memory of the event.
- Sleep-related events have been reported with other hypnotics, but the pattern of reports with zolpidem has been interpreted by the TGA as signalling increased risk with this medicine. While these behaviours are considered rare, the incidence is uncertain. A causal link between zolpidem and these behaviours has not been established.
- If a sleep-related event occurs during use of zolpidem (or another hypnotic), stop the medicine to avoid potential harms to the patient and the community.
- Sleep-related events can occur with therapeutic doses of zolpidem in people without predisposing factors. However, the risk is probably increased by alcohol, other CNS depressants, and high doses of zolpidem.

Trouble du comportement en sommeil paradoxal

TCSP



Trouble du comportement en sommeil paradoxal

TCSP



Trouble du comportement en sommeil paradoxal

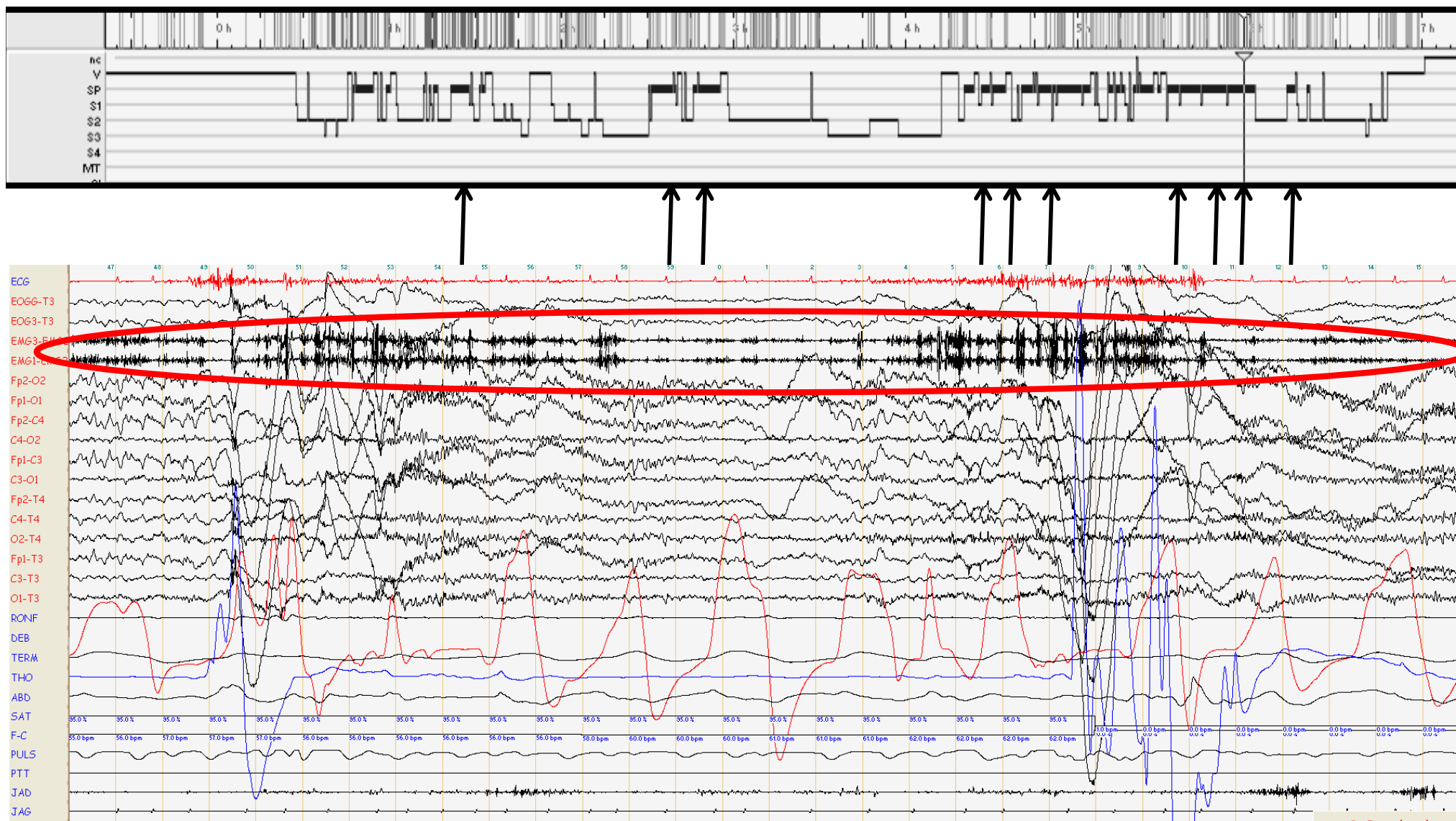
Caractéristiques cliniques :

- Agitation en rapport avec le contenu du rêve
- Souvent violents (coups, cris...)
- Survenue majoritairement en fin de nuit
- Le sujet se souvient d'un rêve cohérent avec les actes réalisés pendant l'épisode

Terrain préférentiel :

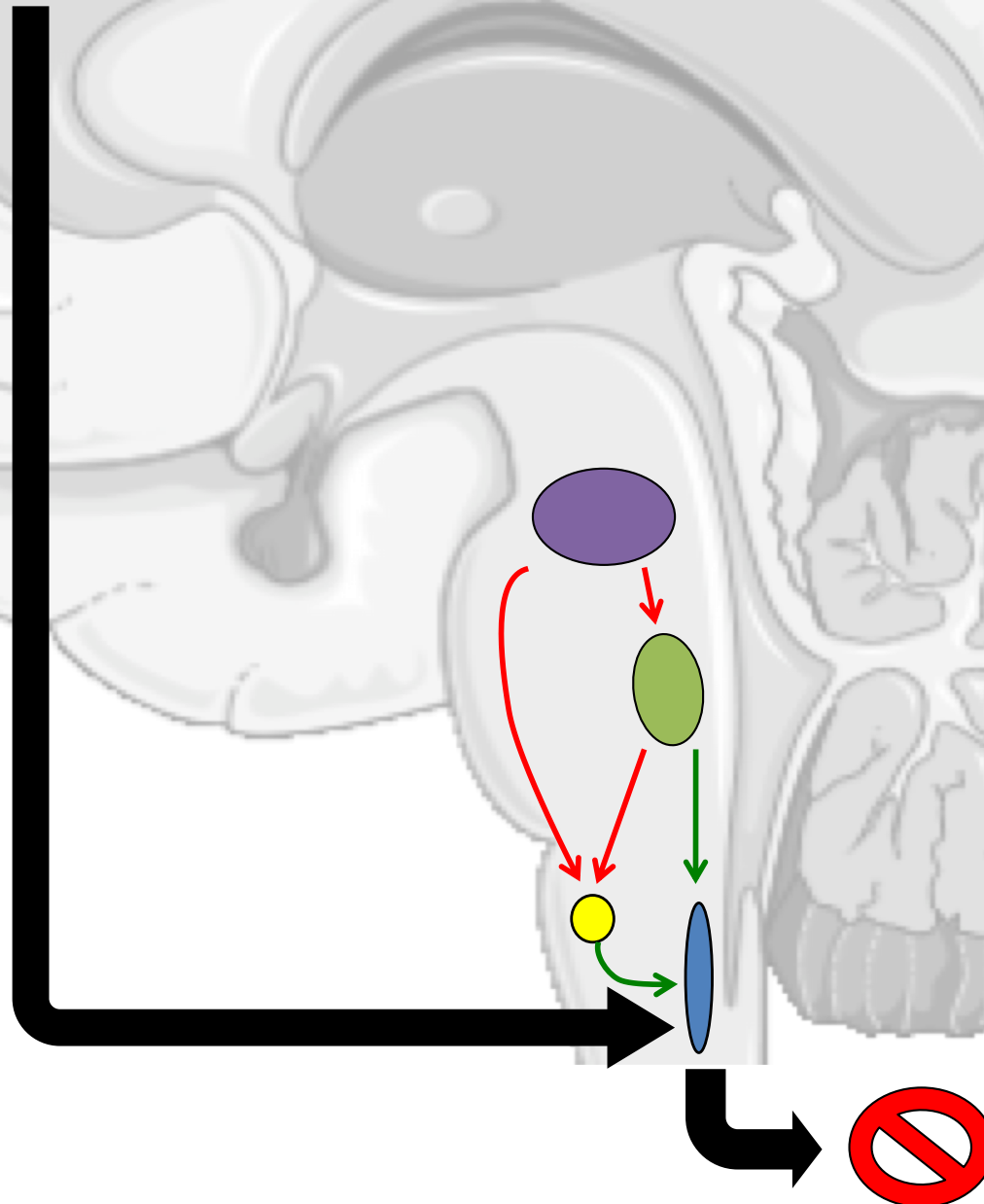
- Essentiellement chez les sujets de plus de 50 ans
- Majoritairement des hommes
- Facteur de risque majeur de pathologie neurodégénérative / Stade précoce de la maladie?

Perte d'atonie en sommeil paradoxal



PHYSIOLOGIE DE L'ATONIE MUSCULAIRE EN SOMMEIL PARADOXAL

CORTEX MOTEUR



Locus subcoeruleus / SLD

Noyau gigantocellulaire / VMM

Noyau rouge

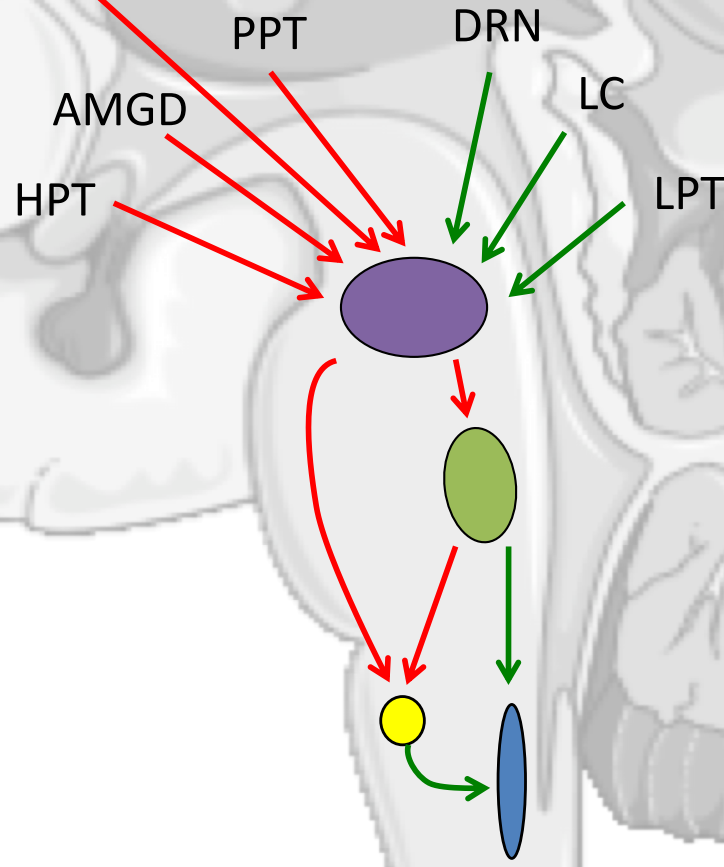
Interneurones spinaux

Motoneurones spinaux

ATONIE MUSCULAIRE

PHYSIOLOGIE DE L'ATONIE MUSCULAIRE EN SOMMEIL PARADOXAL

CORTEX



AMGD = amygdale
HPT = hypothalamus
PPT = tegmentum pediculopontin
DRN = raphé dorsal
LC = locus coeruleus
LPT = tegmentum pontin latéral

Locus subcoeruleus / SLD

Noyau gigantocellulaire / VMM

Noyau rouge

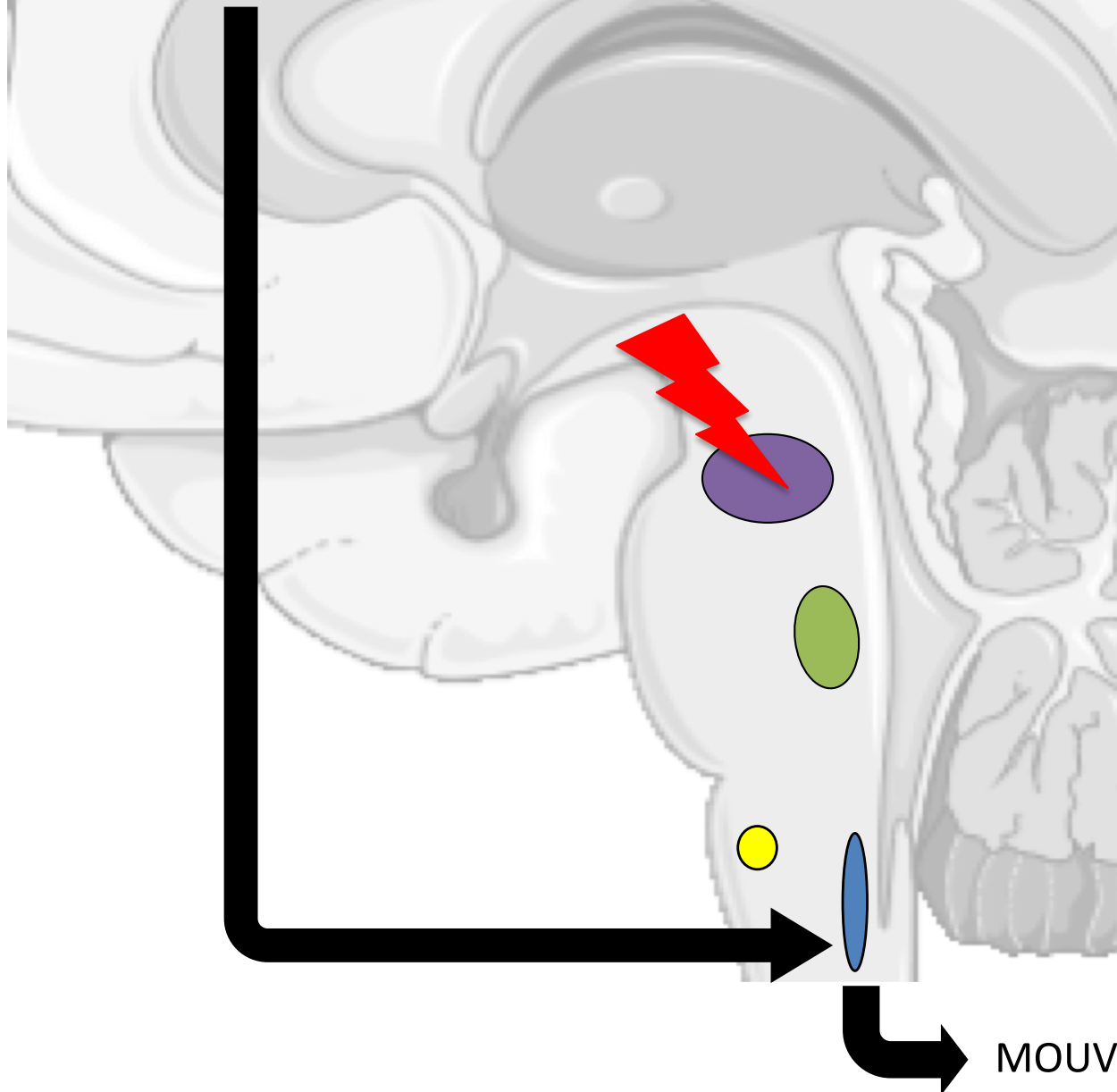
Interneurones spinaux

Motoneurones spinaux

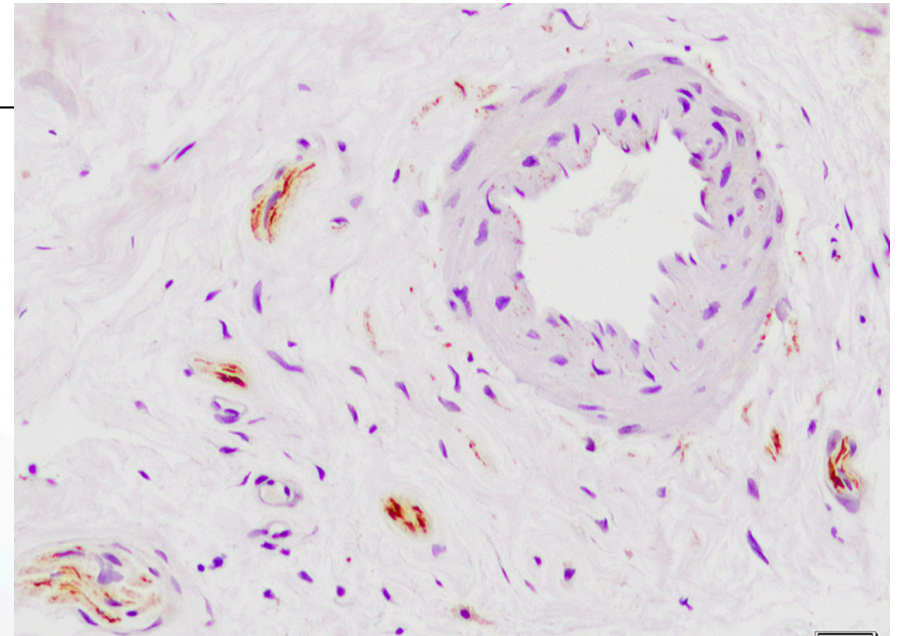
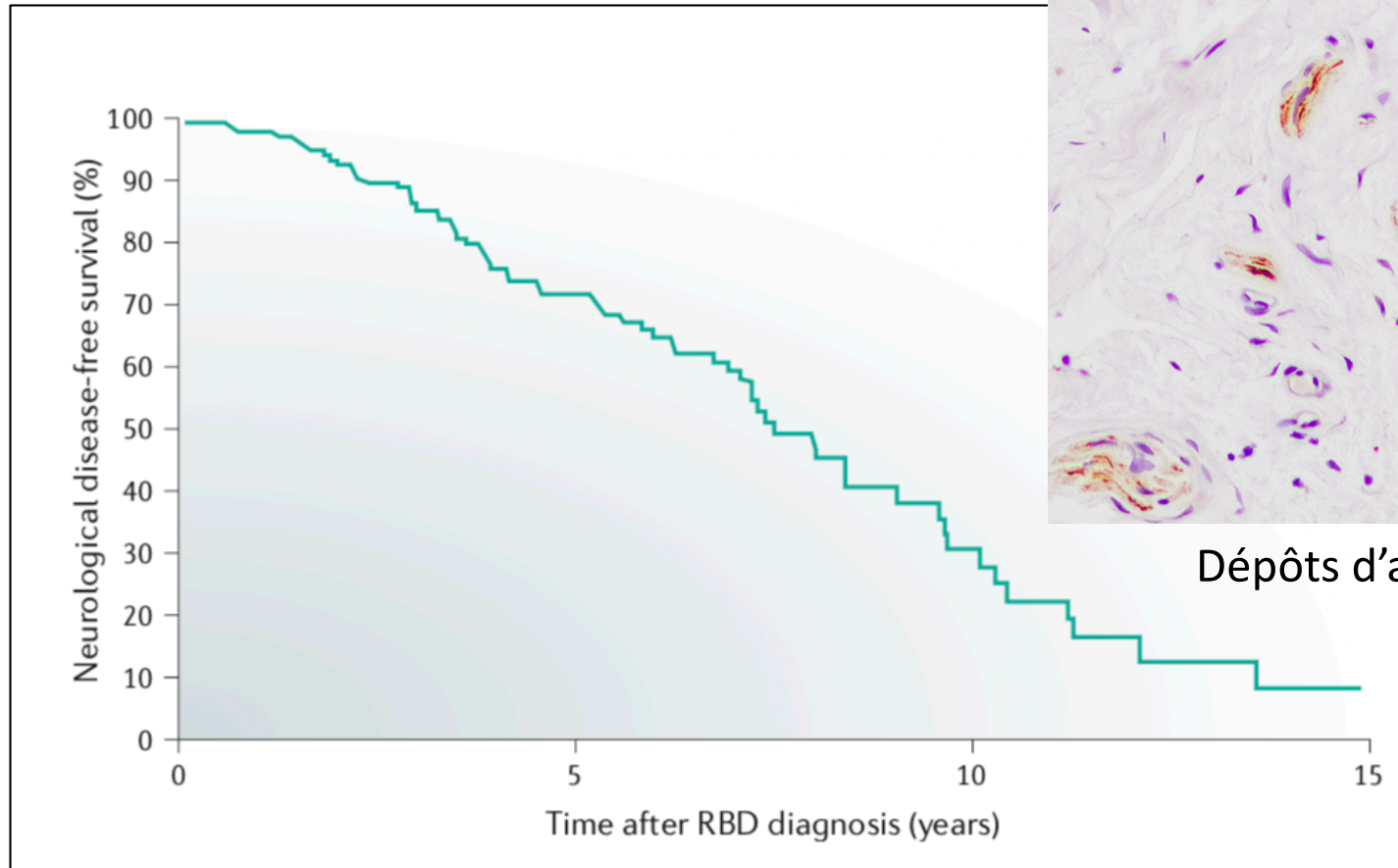
MODELE PHYSIOPATHOLOGIQUE

TCSP

CORTEX MOTEUR

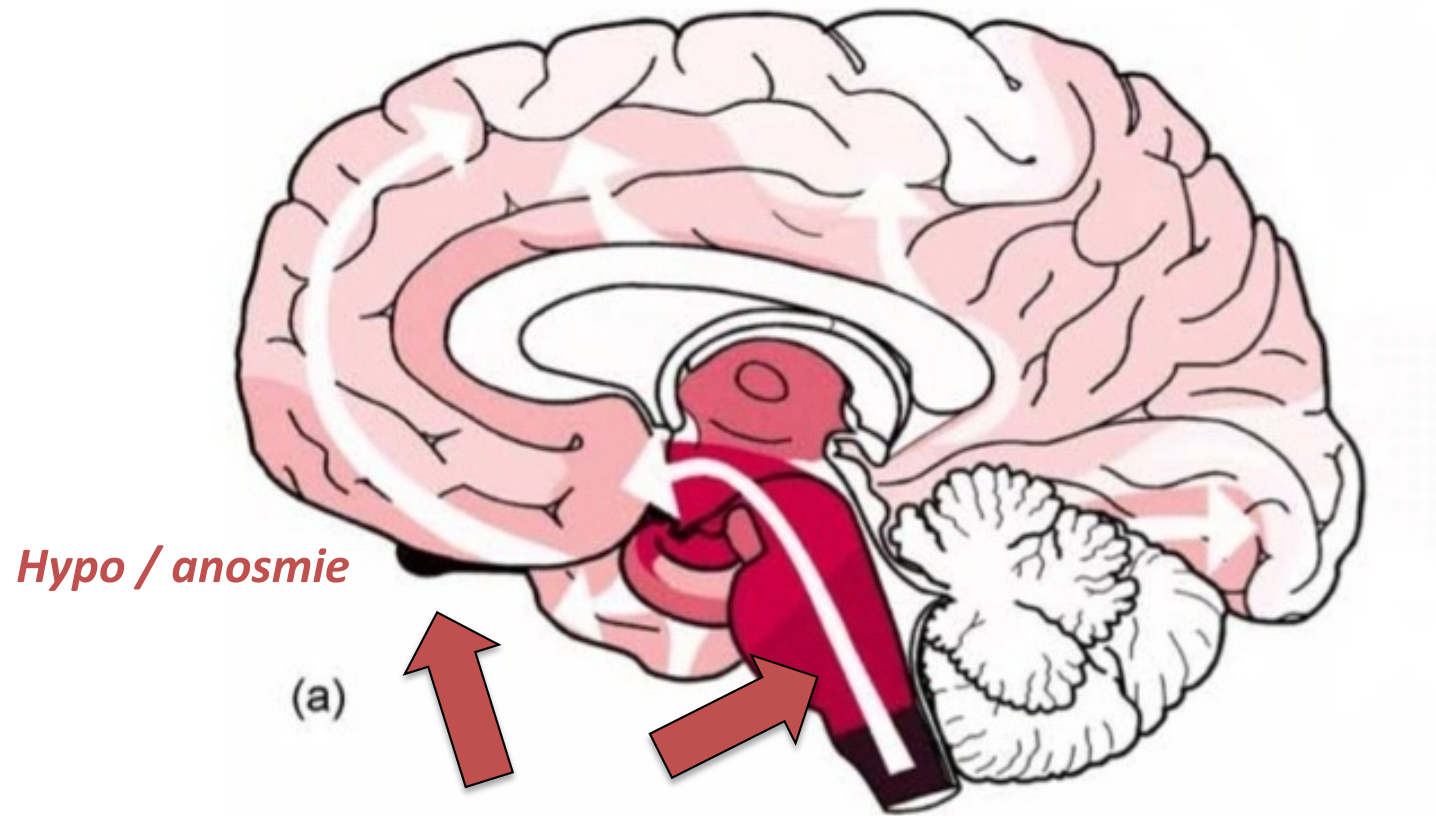


TCSP IDIOPATHIQUE ?



Dépôts d'alpha synucléine dans les glandes salivaires

80% de progression vers une synucléinopathie à 10 ans



Hypo / anosmie

(a)

Stades de Braak 1/2

*Dysautonomie
(Dénervation noradrénergique MIBG)*

TCSP et iatrogénie

Nombreux rapport de cas dans la littérature incriminant la prise d'antidépresseur et la survenue ou l'aggravation de TCSP :

- **Clomipramine** (*Bental et al. 1979, Niyama et al. 1993*)
- **Fluoxetine** (*Schenck et al. 1992*)
- **Mirtazapine** (*Onofrj et al. 2003*)
- **Venlafaxine** (*Schutte et al. 1996*)

TCSP et antidépresseurs

- Etudes systématiques :

- Yo-El Ju et al. 2011***

- 115 sujets TCSP
 - 46,1% de sujets sous antidépresseurs (ISRS, IRSNa, ADTC, NaSSA...)

- Lam et al. 2008***

- 1235 patients souffrant de troubles psychiatriques suivis en ambulatoire
 - 30 sujets présentant un TCSP
 - 86,7% des sujets TCSP reçoivent un antidépresseur (70% un ISRS) contre 49,3% pour les sujets sans parasomnie

TCSP et antidépresseurs

Winkelman et al. 2004

Etude comparative 15 sujets prenant un ISRS ou IRSNa et 15 sujets témoins

Table 2—Submental and Anterior-Tibialis Characteristics in Antidepressant and Control Groups

Epochs, %	Control (n = 15)	Serotonergic Antidepressant (n = 15)	<i>P</i> value
30-second with submental EMG tone*	2.36 ± 3.88	9.54 ± 9.06	.02
2-second with phasic EMG†			
Submental	5.63 ± 5.31	10.74 ± 9.16	.07
Anterior tibialis	9.72 ± 8.64	16.82 ± 14.69	.09
10-second with long EMG‡			
Submental	6.71 ± 6.06	13.39 ± 11.62	.03
Anterior tibialis	2.98 ± 2.63	8.94 ± 12.59	.06

TCSP et antidépresseurs

The Prevalence and Characteristics of REM Sleep without Atonia (RSWA) in Patients Taking Antidepressants

Kenneth Lee, MD; Kelly Baron, PhD; Rodolfo Soca, MD; Hrayr Attarian, MD

JCSM
Journal of Clinical
Sleep Medicine

1444 sujets sous AD vs 10746 sans AD

- TCSP clinique = 0,48% vs 1% (NS)
- Perte d'atonie en SP = 12,2% vs 2,1%

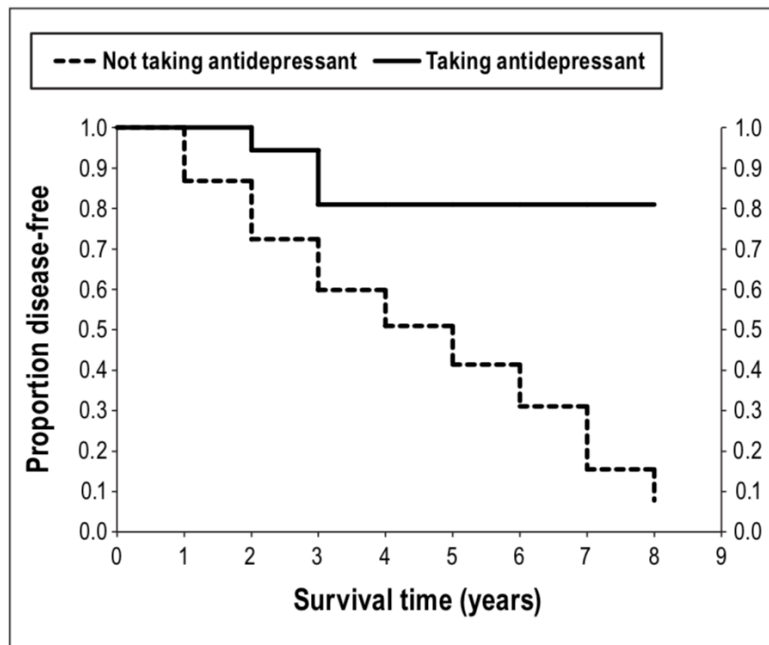
SSRI Type	Total Patients on SSRI/SNRI n (%)	SSRI/SNRI Patients with RSWA n (%)*
Citalopram	210 (13.9)	31 (17.3)
Desvenlafaxine	25 (1.6)	2 (1.1)
Duloxetine	241 (15.9)	29 (16.2)
Escitalopram	339 (22.4)	35 (19.6)
Fluoxetine	175 (11.5)	26 (14.5)
Fluvoxamine	4 (0.3)	0 (0.0)
Paroxetine	61 (4.0)	5 (2.8)
Sertraline	280 (18.5)	37 (20.7)
Venlafaxine	181 (11.9)	14 (7.8)

ANTIDEPRESSANTS AND REM SLEEP BEHAVIOR DISORDER

<http://dx.doi.org/10.5665/sleep.3102>

Antidepressants and REM Sleep Behavior Disorder: Isolated Side Effect or Neurodegenerative Signal?

Ronald B. Postuma, MD, MSc^{1,2}; Jean-Francois Gagnon, PhD^{2,3}; Maria Tuineaig, BSc²; Josie-Anne Bertrand, PhD^{2,4}; Veronique Latreille, PhD^{2,4}; Catherine Desjardins, PhD²; Jacques Y. Montplaisir, MD, PhD^{2,5}



Moins d'évolution vers une pathologie
neurodégénérative

Trouble dissociatif lié au sommeil



Trouble dissociatif lié au sommeil



Trouble dissociatif lié au sommeil

- Episodes complexes, sans souvenirs
- EEG de veille
- Enfants > adultes
- Souvent peu après l'endormissement
- Manifestations de type « trouble dissociatif de l'identité »
- Contexte d'ESPT

Conclusion

- Agitation nocturne :
 - Sommeil lent profond = « somnambulisme, TN »
 - Sommeil paradoxal = « Mise en acte des rêves »
 - Veille = « trouble dissociatif »
- = Pathologies parfois sévères et handicapantes
- Risque élevé d'éveils confusionnels sous zolpidem (1 patient/20)
- TCSP sous antidépresseur



MERCI