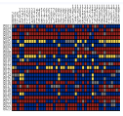
Prise en Charge des Hypersomnolences centrales



Pr Yves Dauvilliers

Centre de Référence Nationale Narcolepsie, Hypersomnies Rares
INSERM U1061, Montpellier, France

Conflit d'intérêt avec UCB Pharma, Avadel, JAZZ, Takeda, Idorsia, Orexia, et Bioprojet. (Article L4113-13)

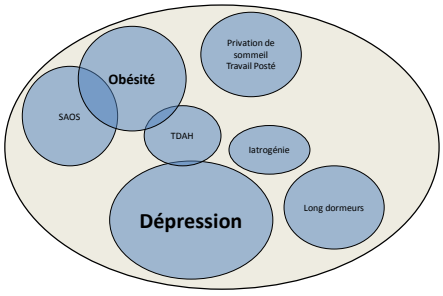
Sommeil et HyperSomnolence

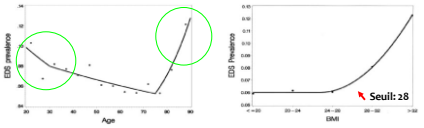
- **Sommeil**
  - **3ième indicateur de bonne santé le plus important (… Stress, Alimentation)**
  - **1/3 de notre vie à dormir …**

HyperSomnolence

Complaint	**Quantité excessive de sommeil "Hypersomnie"** • Excès de sommeil de nuit>9-10 ? • Accès de sommeil le jour >1h ? • Nuit et Jour : >10, 11H ?	**Altération de la qualité de la veille *via incapacité à maintenir une vigilance normale*** • Difficultés à rester éveillé le jour • Endormissements en condition monotone • Attaques de sommeil en condition active
Causes	**IH, long sleepers, depression? …**	**NT1, NT2, IH, OSAS, sleep deprivation…**

Principales Causes d'HyperSomnolence?





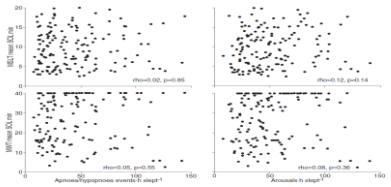
Parameter	ES	*P*	OR
Depression	10.6	<0.001	6.85
Log BMI (kg/m²)	4.3	<0.001	
+1 SD			1.45
+2 SD			2.10
Age	3.6	<0.001	
+1 SD			0.61
+2 SD			0.38
Typical sleep duration	3.2	0.001	
+1 SD			0.76
+2 SD			0.58
Diabetes (glucose > 126)	2.3	0.019	1.87
Smoke	1.9	0.060	1.53
OHI > 15	1.2	0.255	1.70

Plainte de SDE: Non mesurée via tests objectifs Bixler, et al. 2005

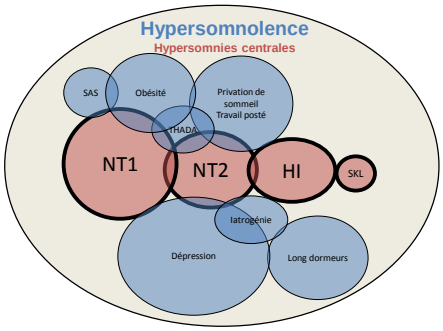
Does arousal frequency predict daytime function?

R.N. Kingshott*, H.M. Engleman*, I.J. Deary, N.J. Douglas*

150 sujets apnéiques (AHI >5/h), Age moyen 50 (22-71), IMC 32 (20-64), ESS 12 (0-24)
AHI 45 (7-144), TILE: 9,7 (2,5-20), TME 27 (2,6-40)

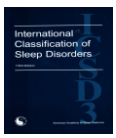


Absence de corrélation entre TILE-TME-ESS, AHI et microéveils
Autres études: Résultats similaires pour Dépression, IMC, Age



Hypersomnolences centrales = Maladies Rares

- **Narcolepsie type 1:** *Hypocrétine déficient*
- **Narcolepsie type 2**
- **Hypersomnie idiopathique**
- Syndrome de Kleine-Levin



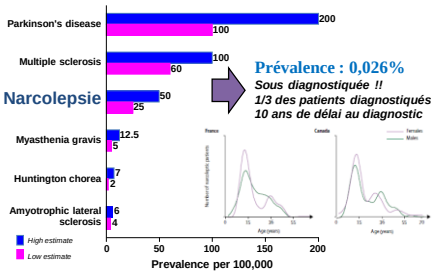
- **Causes d'Hypersomnolence les plus sévères chez l'homme**
  - **Modèles pour comprendre la régulation du sommeil**
  - **Permet le développement de médicaments innovants**

Sleep disorders in neurology

French consensus. Hypersomnolence: Evaluation and diagnosis

Y. Dauvilliers[a,b,c,*], R. Lopez[a,b,c], M. Lecendreux[a,d]

Narcolepsie type 1: Maladie Rare



Billiard and Dauvilliers. In: *Sleep, Physiology, Investigations and Medicine*. New York 2003; Dauvilliers et al Neurology 2001

Narcolepsie-Cataplexie: Symptômes

- **Rarement familial**
- **Age début: 15 ans**
- **SDE**
  - Accès de sommeil courts itératifs rafraîchissant incohercibles avec une activité onirique associée
  - Symptôme le plus invalidant

- **Cataplexie**
  Perte du tonus musculaire déclenchée par une émotion positive
- Hallucinations hypnagogiques, paralysies du sommeil
- Mauvais sommeil de nuit et agitation nocturne, surpoids, depression, puberté précoce…

➡ **Dysrégulation du sommeil paradoxal: Jour et Nuit**

Cataplexie

= Spécifique de la narcolepsie
= Meilleur marqueur diagnostic

Diagnostic de la cataplexie est essentiellement clinique

- History of sudden muscle weakness
  - Partial: buckling of the knees, laxity of the neck or jaw muscles
  - Total: complete loss of muscle tone
- Triggered by emotional factors,
  - Often by positive emotions (laughter, joking…)
  - Almost never by stress, fear or physical effort
- Fully conscious during the episode.
- Deep tendon reflexes are transiently abolished during generalized cataplexy
- Duration of cataplexy varies from a second to one or two minutes.
- Frequency varies from < 1 episode/y to several episodes / day.

Clinical forms

- "status cataplecticus" with continual cataplectic episodes, lasting several hours (in cases of withdrawal of anticataplectics !!)

Complex movement disorders at disease onset in childhood narcolepsy with cataplexy

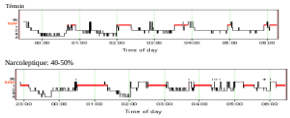
Brain 2011

Giuseppe Plazzi,[1] Fabio Pizza,[1] Vincenzo Palaia,[1] Christian Franceschini,[1] Francesca Poli,[1] Keivan K. Moghadam,[1] Pietro Cortelli,[1] Lino Nobili,[2] Oliviero Bruni,[3] Yves Dauvilliers,[4] Ling Lin,[5] Mark J. Edwards,[6] Emmanuel Mignot[5] and Kailash P. Bhatia[6]

Phénomène moteur négatif | **Phénomène moteur positif**

ICSD-3 Narcolepsie Type 1, Narcolepsie-cataplexie
Syndrome hypocrétine déficient

A. Plainte de SDE depuis plus de 3 mois
B. Présence de un ou 2 items
   A. Cataplexie ET TILE ≤ 8 min et ≥ 2 SOREMPs (incluant possible SOREM de nuit: < 15 min)
   B. LCR: **Hypocrétine** ≤ 110 pg /ml en RIA

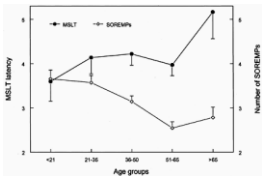


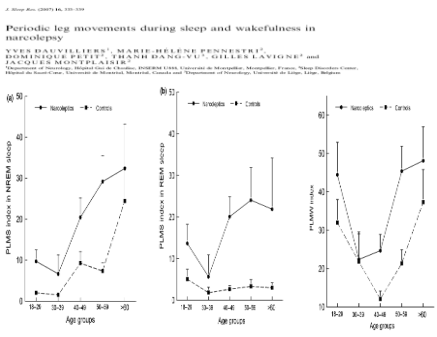
Enregistrement du sommeil

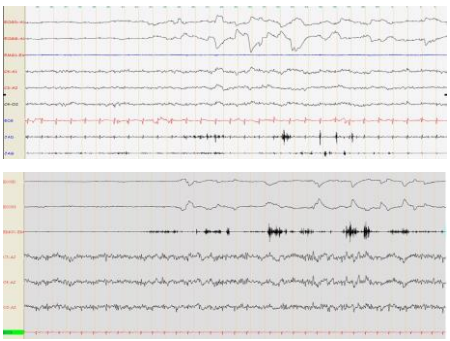
Polysomnographie
- Elimine les autres causes de SDE
- Nécéssite la présence d'une durée suffisante de sommeil (> 6h)
- Beaucoup de stade 1, SLP en fin de nuit, peu de fuseaux de sommeil
- Mouvements périodiques fréquents
- Possible SAOS associé
- Sommeil paradoxal: latence courte et souvent SP dissociée

TILE: **Latence < 8 min**
≥ 2 SOREMPs.

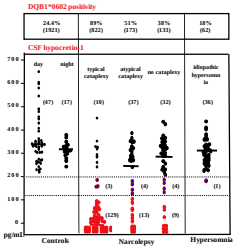
MSLT and narcolepsy: Age effect
Dauvilliers et al
Neurology 2004; 62: 46-50





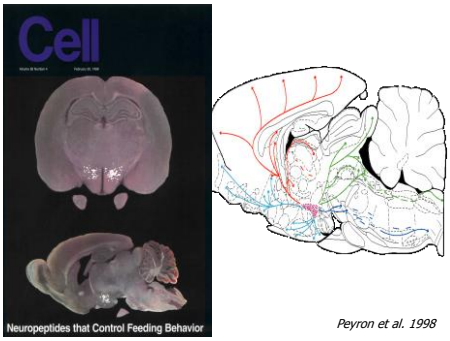


CSF Hypocretin-1 / Orexine-A levels
Clinical indications for measurement



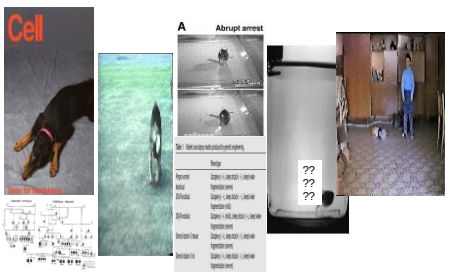
Dauvilliers et al Lancet 2007

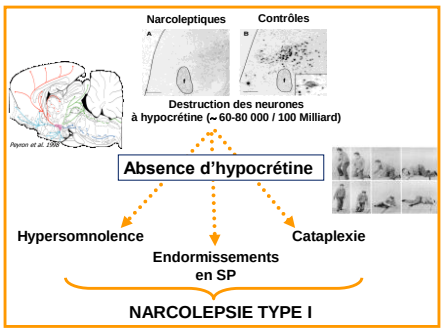
- Atypical MSLT results (e.g., a long mean sleep latency or one SOREMP on the MSLT).
- Comorbid psychiatric, neurological, or medical disorders … or with atypical cataplexy
- Psychotropic medications (e.g., anticataplectics or stimulants) that cannot be stopped!
- Young children who are unable to follow MSLT instructions, but limitations due to ethical issues.



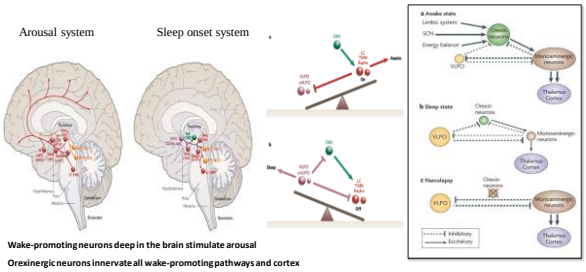
Peyron et al. 1998

Narcolepsies et Cataplexies existent dans de nombreuses espèces animales





Normal regulation of sleep and wake systems

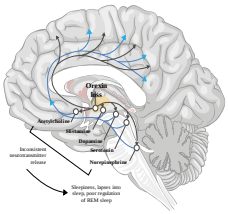


Wake-promoting neurons deep in the brain stimulate arousal

Orexinergic neurons innervate all wake-promoting pathways and cortex

During sleep these neurons are inhibited by NT released from preoptic area neurons

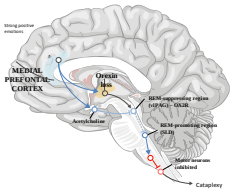
Orexin neuron loss results in sleepiness in NT1



Reduced orexin excitatory input to cortex, thalamus, wake-promoting neurotransmitter systems results in sleepiness and abnormal REM sleep regulation

Scammell TE. *N Engl J Med.* 2015;373:2654–2662.

Cataplexy result from reduced activity in REM sleep-inhibiting brain regions in NT1

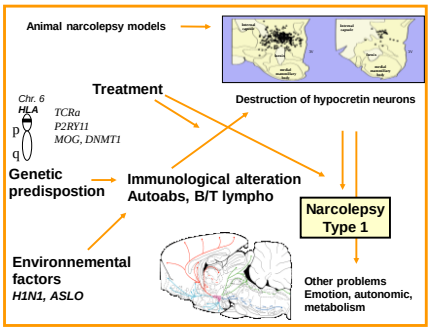


Emotions activate neurons in mediorefrontal cortex that excite orexin neurons / amygdala

Loss of ORX excitatory input to the vlPAG that "normally" suppresses REM sleep

Activation of SLD neurons that promotes REM sleep that inhibit motoneurons: **Cataplexy**

Scammell TE. *N Engl J Med.* 2015;373:2654–2662.



- **Cas sporadiques > 98 %** ➞ Forte association HLA DQB1*0602: >92%
  Hypocrétine déficient
  Effet d'autres gènes immuns: TCR…
  Autoimmunité: Ly CD4+ et CD8+
  Importance de l'environnement:H1N1, strepto

- **Cas familiaux 1-2 %** ➞ Faible HLA DQB1*0602 positivité
  Hypocrétine déficient ?
  Rare mutations: préprohcrt, MOG, DNMT1, NPC, P2RY11…

➞ **Pathophysiologie hétérogène! Précision**

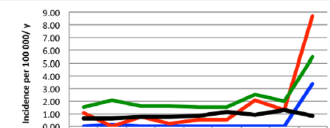
Rôle de l'environnement ++

Vaccin H1N1: Risque augmenté de 5-14 chez Enfants et 2-7 Adultes

~ 120 dossiers en cours d'Expertise en France à ONIAM

Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland

Markku Partinen[1,2,15], Outi Saarenpää-Heikkilä[3], Ismo Ilveskoski[4], Christer Hublin[5], Miika Linna[6], Päivi Olsén[7], Pekka Nokelainen[8], Reija Alén[9], Tiina Wallden[10], Merimaaria Espo[10], Harri Rusanen[11], Jan Olme[12], Heli Sätilä[13], Harri Arikka[14], Pekka Kaipainen[15], Ilkka Julkunen[16], Turkka Kirjavainen[17]



	2002	2003	2004	2005	2006	2007	2008	2009	2010
< 11 y	0.00	0.15	0.00	0.00	0.00	0.00	0.00	0.00	3.39
11 -16 y	1.04	0.00	0.76	0.25	0.50	0.51	2.08	1.33	8.67
17-19 y	1.50	2.07	1.59	1.59	1.56	1.52	2.51	1.97	5.46
20+ y	0.63	0.63	0.77	0.77	0.81	1.13	0.93	1.26	0.87

BRAIN

Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France

Yves Dauvilliers,[1,2] Isabelle Arnulf,[2,3] Michel Lecendreux,[2,4] Christelle Monaca Charley,[5] Patricia Franco,[2,6] Xavier Drouot,[7] Marie-Pia d'Ortho,[8] Sandrine Launois,[9] Séverine Lignot,[10] Patrice Bourgin,[11] Béatrice Nogues,[12] Marc Rey,[13] Sophie Bayard,[1,2] Sabine Scholz,[1,2] Sophie Lavault,[2,3] Pascale Tubert-Bitter,[14] Cristel Saussier[15] and Antoine Pariente[15] on behalf of the Narcoflu-VF study group

France: Octobre 2009 – Février 2010: 5,7 M vaccinés: 8,8% de population générale

4.1 M Pandemrix® : 89% des sujets > 9 ans

1.6 M Panenza® (sans adjuvant): Enfants < 9 ans, grossesse, immunodépression…)

	Cases n = 59	Controls n = 135	P
Infections			
Infectious episodes, between 1 January 2005 and index date, n (%)	47 (79.7)	112 (83.0)	0.18
Confirmed Epstein-Barr Virus infection between 1 January 2005 and index date, n (%)	2 (4.3)	2 (1.8)	0.37
Confirmed streptococcal infection between 1 January 2005 and index date, n (%)	0	4 (3.6)	0.45
Upper respiratory tract infectious episode between 1 January 2005 and index date, n (%)	39 (83.0)	99 (88.4)	0.20
Gastrointestinal tract infectious episode between 1 January 2005 and index date, n (%)	12 (25.5)	50 (44.6)	0.07
Flu-like episode during the last two flu seasons preceding index date, n (%)	13 (22.0)	24 (17.8)	0.20
Vaccinations			
At least one seasonal influenza vaccination between 1 January 2005 and index date, n (%)	5 (8.5)	23 (17.0)	0.12
H1N1 influenza vaccination, n (%)	31 (52.5)	24 (17.8)	<10 [-4]
Pandemrix®	27	17	
Panenza®	4	1	
Undocumented	0	6	
Non-flu vaccinations during the past 2 years, n (%)	15 (25.4)	45 (33.3)	0.37
Non-flu vaccinations between 1 January 2005 and index date, n (%)			
Diphteria	38 (84.4)	80 (80.8)	0.68
Tetanus	40 (88.9)	83 (83.8)	0.50
Poliovirus	38 (84.4)	80 (80.8)	0.68
Haemophilus influenza type B	7 (15.6)	9 (9.1)	0.39
Pertussis	19 (42.2)	41 (41.4)	0.76
Hepatitis B	6 (13.3)	25 (25.3)	0.79
Human papilloma virus	3 (5.1)	7 (5.2)	0.42

➞ **Phénotype identique entre sujets vaccinés et non vaccinés H1N1**

Narcolepsy Onset Is Seasonal and Increased following the 2009 H1N1 Pandemic in China

Fang Han, MD,[1] Ling Lin, MD, PhD,[2] Simon C. Warby, PhD,[2] Juliette Faraco, PhD,[2] Jing Li, BS,[1] Song X. Dong, MD,[1] Pei An, BS,[1] Long Zhao, BS,[1] Ling H. Wang, MD,[1] Qian Y. Li, MD,[1] Han Yan, MD,[1] Zhan C. Gao, MD,[1] Yuan Yuan, MD,[1] Kingman P. Strohl, MD,[3] and Emmanuel Mignot, MD, PhD[2]

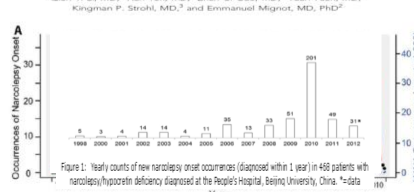


Figure 1: Yearly counts of new narcolepsy onset occurrences (diagnosed within 1 year) in 468 patients with narcolepsy/hypocretin deficiency diagnosed at the People's Hospital, Beijing University, China. *=data

➞ Augmentation du risque de Narcolepsie en 2009/2010, **OR: 3,2**
Pas de vaccination H1N1 !!

Genome-wide association study identifies new HLA class II haplotypes strongly protective against narcolepsy

Chr. 6	Complex HLA	Region DQ/DR	Serology	DNA

p — Class I — Class III — q

DRB1 → DR2 → DR15 → DRB1*1501 (Blancs et asiatiques) ; DR16 → DRB1*1503 (Afro-Américains)

DQA1 → DQ1 → DQ6 → DQB1*0602 ; DQ5 → DQA1*0102 (Tout groupe ethnique)

Class II : DR, DQ, DP

> 97% : association

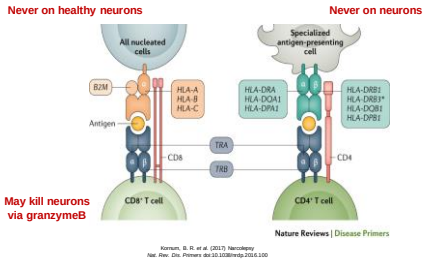
Narcolepsy: HLA disease++ (OR >250)

HLA-DQB1*0603: Protector allele (OR: 0,17) (as DQB1*05:01, 06:01)

Function of HLA

To present epitopes to Lympho T receptors

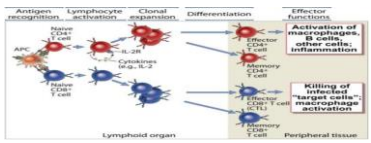
Immune adaptative response

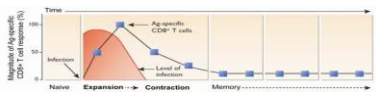


Konnum, B. R. et al. (2017) Narcolepsy
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.100

Nouveaux Biomarqueurs = Immunologie !!

Réponses des Lymphocytes T



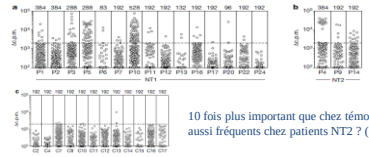


Résultats dans Narcolepsie de type I ?

T cells in patients with narcolepsy target self-antigens of hypocretin neurons

16 NT1 / 3 NT2 / 13 Témoins

Clone de Lympho T sanguin: Détection **Ly T CD4+ mémoire spécifique Hypocrétin**



10 fois plus important que chez témoins aussi fréquents chez patients NT2 ? (NT2-1)

Détection Lympho T CD4+ mémoire spécifique Hypocrétine Polyclonaux (rares T CD8+)

Absence de lien avec Influenza

Argument fort autoimmun dans narcolepsie: Diagnotic rapide/ Immunotherapie ?

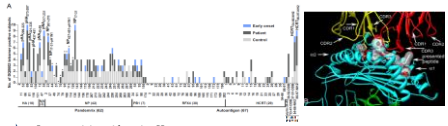
Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy

PNAS | vol. 115 | no. 52 | E12323–E12332

Guo Luo[a], Aditya Ambati[b,c], Ling Lin[a,1], Mélodie Bonvalet[a], Markku Partinen[b,c], Xuhuai Ji[d], Holden Terry Maecker[d], and Emmanuel Jean-Marie Mignot[a,2]

Screening of 15-mer peptides that bind to DQ 06:02 CD4 + Lymph T
(Tetramers for detection: 0.02% clones): 35 NT1 and 22 HLA + controls

Cross reactivity with
- pHA273-287 (H1N1 specific)
- NP
- C-terminal Amidated Hcrt54-56 /86-97 with glycine (not naive form)

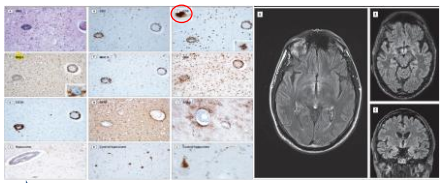


Low reactivity with native Hcrt
Reactivity with post amidated Hcrt and peptides of H1N1
Autoimmune process on post-translational proteins (immune tolerance via Thymus)
CDR3 specific sequence of TCRalpha for autoAg binding presented by HLA

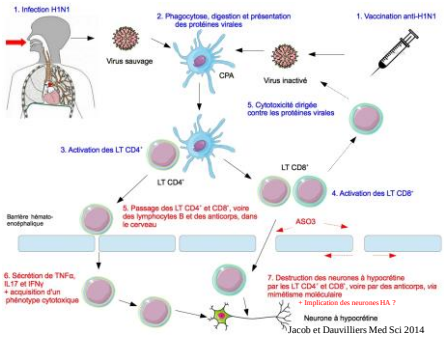
Hypothalamic Immunopathology in Anti-Ma–Associated Diencephalitis With Narcolepsy-Cataplexy

Yves Dauvilliers, MD, PhD; Jan Bauer, PhD; Valérie Rigau, MD, PhD; Nicole Labruyere, MD; Pierre Labauge, MD, PhD; Bertrand Carlander, MD; Roland Liblau, MD, PhD; Christelle Peyron, PhD; Hans Lassmann, MD

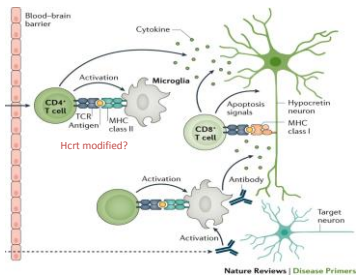
A 63-y.o man diencephalic/brainstem encephalitis: Secondary NT1, No hcrt, **Ma2+**
Death occurred 4 months after disease onset, no tumor



Major inflammation in hypothalamus: Cytotoxic CD8+ T lympho
No more hypocretin neurons

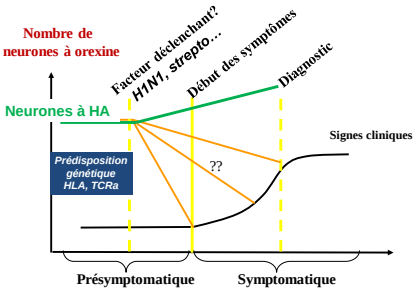


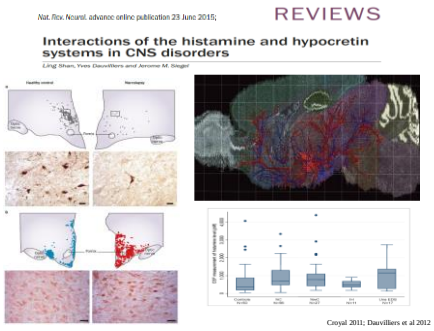
Jacob et Dauvilliers Med Sci 2014



Xonsun, B. R. et al. (2017). Narcolepsy
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.100

Modèle Physiopathologique de NT1



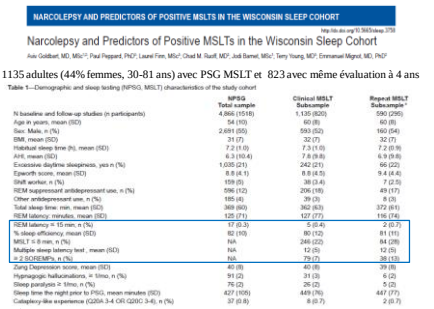


Croyal 2011; Dauvilliers et al 2012

ICSD-3 Narcolepsie Type 2 ou Narcolepsie sans Cataplexie

1. Plainte de SDE depuis > 3
2. TILE: Latence ≤ 8 min ET ≥2 SOREMPs (incluant possible SOREM de nuit)
3. Cataplexie absente
4. LCR hypocrétin-1 > 110 pg /ml ou non mesurée
5. Pas d'explication autre de la SDE: SAS, Privation de sommeil, retard de phase, traitements (prise ou sevrage)

Prévalence ???: 1-4%....



1135 adultes (44% femmes, 30-81 ans) avec PSG MSLT et 823 avec même évaluation à 4 ans

Table 1—Demographic and sleep testing (NPSG, MSLT) characteristics of the study cohort

	NPSG Total sample	Clinical MSLT Subsample	Repeat MSLT Subsample[a]
N baseline and follow-up studies (n participants)	4,866 (1518)	1,135 (820)	590 (295)
Age in years, mean (SD)	54 (10)	60 (8)	60 (8)
Sex: Male, n (%)	2,691 (55)	593 (52)	160 (54)
BMI, mean (SD)	31 (7)	32 (7)	32 (7)
Habitual sleep time (h), mean (SD)	7.2 (1.0)	7.3 (1.0)	7.2 (0.9)
AHI, mean (SD)	6.3 (10.4)	7.8 (9.8)	6.9 (9.6)
Excessive daytime sleepiness, yes n (%)	1,035 (21)	242 (21)	66 (22)
Epworth score, mean (SD)	8.8 (4.1)	8.8 (4.5)	9.4 (4.4)
Shift worker, n (%)	159 (5)	38 (3.4)	7 (2.5)
REM suppressant antidepressant use, n (%)	596 (12)	206 (18)	49 (17)
Other antidepressant use, n (%)	185 (4)	39 (3)	8 (3)
Total sleep time: min, mean (SD)	369 (60)	362 (63)	372 (61)
REM latency: minutes, mean (SD)	125 (71)	127 (77)	116 (74)
REM latency ≤ 15 min, n (%)	17 (0.3)	5 (0.4)	2 (0.7)
% sleep efficiency, mean (SD)	82 (10)	80 (12)	81 (11)
MSLT ≤ 8 min, n (%)	NA	246 (22)	84 (28)
Multiple sleep latency test , mean (SD)	NA	12 (5)	12 (5)
≥ 2 SOREMPs, n (%)	NA	79 (7)	38 (13)
Zung Depression score, mean (SD)	40 (8)	40 (8)	39 (8)
Hypnagogic hallucinations, ≥ 1/mo, n (%)	91 (2)	31 (3)	6 (2)
Sleep paralysis ≥ 1/mo, n (%)	76 (2)	26 (2)	5 (2)
Sleep time the night prior to PSG, mean minutes (SD)	427 (105)	449 (76)	447 (77)
Cataplexy-like experience (G20A-3-4 OR G20C-3-4), n (%)	37 (0.8)	8 (0.7)	2 (0.7)

Test-retest pour latence au MLST, soremps, soremp de nuit, MSLT+: faible (k : 0,2)

NARCOLEPSY AND PREDICTORS OF POSITIVE MSLTS IN THE WISCONSIN SLEEP COHORT

Narcolepsy and Predictors of Positive MSLTs in the Wisconsin Sleep Cohort

1 sujet avec possible NC et SOREMPs
2 sujets avec 2 MSLT+, sans cataplexie
} Moins de 33% de concordance dg!!
NC: 0,07% et NwC: 0,2%
Facteurs de risque de changement: Travail posté et privation de sommeil

Table 2—Predictors of MSLT abnormalities, cataplexy and NPSG SOREMP, estimated by multiple logistic regression

Models: Outcome Variables	N (%)	Predictor Variables *	Odds Ratio (95% Confidence Interval)	P-value
1) Nocturnal SOREMP - REM latency ≤ 15 minutes	17 (0.4%)	Sleep the night before (1 hour less) Shift work	1.34 (1.02, 1.76) 2.24 (0.54, 9.26)	0.03 0.26
2) ≥ 2 SOREMPs	79 (7%)	Shift work	4.95 (2.35, 10.43)	< 0.0001
3) MSLT ≤ 8 minutes	245 (22%)	Habitual sleep time (1 hour less) Apnea-hypopnea index (5 units)	1.35 (1.15, 1.58) 1.11 (1.02, 1.20)	0.0002 0.002
3.5) MSLT ≤ 8 minutes	245 (22%)	Habitual sleep time, ≤ 6 vs > 6 hours Apnea-hypopnea index 5-15 vs < 5 Apnea-hypopnea index ≥ 15 vs < 5	1.88 (1.24, 2.84) 1.25 (0.88, 1.76) 1.68 (1.09, 2.58)	0.003 0.21 0.02
4) ≥ 2 SOREMPs and MSLT ≤ 8 minutes	38 (3%)	Habitual sleep time (1 hour less) Shift work	1.51 (1.02, 2.23) 7.77 (2.70, 22.39)	0.04 0.0001
5) Nocturnal SOREMP or (≥ 2 SOREMPs and MSLT ≤ 8 minutes)	42 (4%)	Habitual sleep time (1 hour less) Shift work	1.62 (1.05, 2.49) 6.69 (2.23, 20.04)	0.03 0.0007
6) Cataplexy-like experiences, ≤ 1/month **	10 (0.9%) *	Zung score (10 points)	2.50 (1.09, 5.74)	0.03

* All models adjusted for age and sex; ** defined using the OR statement; * sample of 1,124 people who have survey 3 data and PSG within 5 years.

ICSD-3: **Hypersomnie idiopathique,** hypersomnolence/somnie neurologique idiopathique ou primaire, hypersomnie centrale idopathique

1. Besoin de dormir quotidiennement ou endormissement diurne depuis > 3 mois
2. Pas de cataplexie
3. TILE: <2 SOREMPs (incluant SOREM de nuit)
4. Au moins un des éléments:
   1. **TILE: latence ≤ 8 min**
   2. **TTS > 11h/24h via PSG** /actimétrie +agenda de sommeil pdt 7j
5. Eliminer l'insuffisance de sommeil
6. Pas d'explication autre de la SDE: SAS, pathologies médicales ou psychatriques, traitements (prise ou sevrage)

HYPERSOMNIE(S) IDIOPATHIQUE(S)

- Pathologie(s) assez mal définies
- Deux phénotypes différents mais pas de symptômes spécifiques
- Age de début: souvent dans enfance (< 20 ans) mais début insidieux
- Prédominance F, évolution instable, formes familiales fréquentes

Avec allongement du temps de sommeil	• Longue durée de sommeil (> 11 /24h) • Difficulté majeure au réveil: 1 à 3h: automatisme • Somnolence récurrente ou constante • Sommeil de nuit ou jour non rafraîchissant
Sans allongement du temps de sommeil	• Durée de sommeil de nuit normale (>6 et < 10h) • Pas de difficulté majeure à se réveiller • Somnolence récurrente, plus irrésistible • Sommeil de nuit ou jour souvent rafraîchissant • Continuum possible avec narcolepsie sans cataplexie

Evaluation neurologique et psychologique: normale
Cause:? Biomarqueurs ??

Few studies recorded patients with 24-h protocol recording

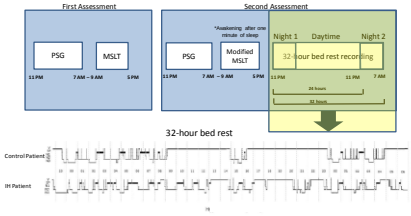
Idiopathic hypersomnia
M. Billiard and Y. Dauvilliers

Idiopathic Hypersomnia with and without Long Sleep Time: A Controlled Series of 75 Patients
Sleep 2009

Daytime continuous polysomnography predicts MSLT results in hypersomnias of central origin
J Sleep Res 2013

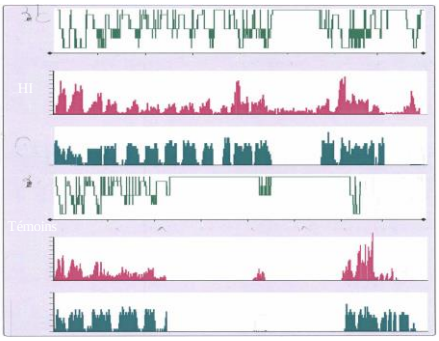
Variable inclusion criteria	Abnormal MSLT or total sleep time ≥11 hours
Lack of validation and standardization	• Level of physical and social activity, lights... • Variable duration: 20 or 24 hours • Invitation to nap or free-running protocol • Ambulatory vs in lab
Variable daytime sleep duration before recording	MSLT preceding or following recording Sleep duration during MSLT

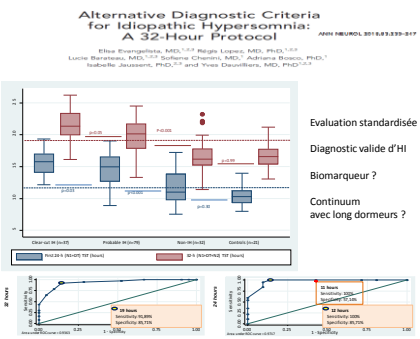
32-Hour Assessment of Idiopathic Hypersomnia



TST cutoff to discriminate IH to controls was **19 hours over 32-hour recording**

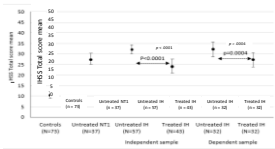
Evangelista E, et al. *Ann Neurol*. 2018;83(2):235-247.





Idiopathic Hypersomnia Severity Scale (IHSS)

- 14-item questionnaire that assesses the severity of IH
  - 5 on nighttime sleep symptoms and related sleep inertia
  - 4 on daytime sleep symptoms and related sleep inertia
  - 5 on daytime function
- Total score 0 to 50, higher score indicating more severe and frequent symptoms



- Higher scores in drug-free patients with IH than NT1 and controls
- No ceiling effect
- **Cut off to discriminate IH and controls: 22**
  Sensitivity: 91.1%
  Specificity: 94.9%
- **Untreated and treated IH: 26**
  Sensitivity: 55.8%
  Specificity: 78.9%
- **Treatment difference:** 5-8 units

IHSS is a reliable, valid clinical tool for the quantification of IH symptoms; sensitive enough to detect clinical changes in symptoms following treatment!

IHSS: Clinically Relevant Score Ranges

Goal:
To confirm its psychometric properties and responsiveness of IHSS to medications
To estimate the minimum clinically important difference
To report clinically relevant score ranges

Component I: 7 items on daytime functioning

Component II: 5 items on long sleep duration and sleep inertia

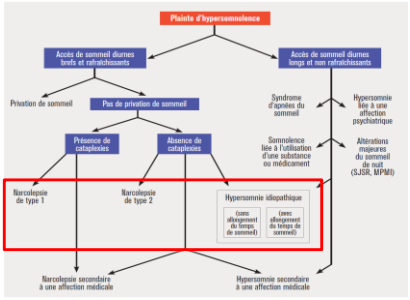
Component III: 2 items on napping

IHSS total score was lower in treated than untreated patients; between-group differences related to treatment.
Probability of having severe EDS, high BDI, low QoL increased with the severity level.

Clinically relevant score ranges
Mild = 0-12
Moderate = 13-25
Severe = 26-38
Very severe = 39-50

These findings should stimulate the use of the IHSS in clinical settings and in research studies

BDI = Beck Depression Index; ESS = excessive daytime sleepiness; QoL = quality of life
Raissi A.L. et al. *J Clin Sleep Med.* 2022;18(2):617-629.



Dauvilliers Y. Diagnostic Algorithm for Hypersomnias. In "Handbook of sleep disorders", 2nd Ed, C Kushida, Informa Healthcare 2008:277-87

Narcolepsie type 1	Narcolepsie type 2	Hypersomnie Idiopathique
Hypersomnolence **Phénotypes différents:** Longues vs courtes siestes, rafraîchissantes ou pas, rêves ou non, attaques de sommeil…		
Cataplexie (rarement sans) Hallucination, Paralysie sommeil, Sommeil perturbé Obésité, puberté précoce	+- HH, PS Sommeil perturbé? Obésité ?	Bon et long temps de sommeil de nuit/jour Inertie du sommeil Parasomnies ?

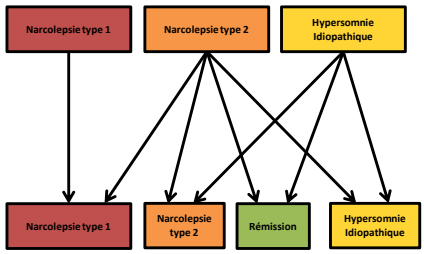
Narcolepsie type 1	Narcolepsie type 2	Hypersomnie Idiopathique
Hypersomnolence **Phénotypes différents:** Longues vs courtes siestes, rafraîchissantes ou pas, rêves ou non, attaques de sommeil…		
Cataplexie (rarement sans) Hallucination, Paralysie sommeil, Sommeil perturbé Obésité, puberté précoce	+- HH, PS Sommeil perturbé? Obésité ?	Bon et long temps de sommeil de nuit/jour Inertie du sommeil Parasomnies ?
TILE < 8 min ≥ 2 SOREMPs	**TILE < 8 min *≥ 2 SOREMPs*** *Exclure privation sommeil*	**TILE < 8 min < 2 SOREMP ou TST >11-12/24h - 19/32h** Inertie du sommeil ? *Exclure privation sommeil*
Déficience en Hypocrétine HLA DQB1*06:02	Pas de biomarqueur !	Pas de biomarqueur !

Narcolepsie SANS cataplexie = TYPE 2
Même critère que narcolepsie….
Hypocrétine normale ds LCR

Hypersomnie idiopathique
Endormissements en sommeil LENT

Mécanismes impliqués ?
Maladies hétérogènes ? instables

Histoire naturelle des Hypersomnies Centrales

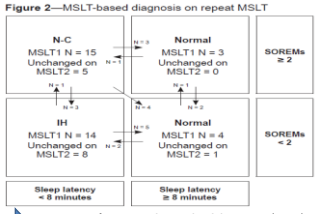


HI et NT2: Maladies polymorphes, instables: Pathogénie?

Test-Retest Reliability of the Multiple Sleep Latency Test in Narcolepsy without Cataplexy and Idiopathic Hypersomnia

Population clinique avec test-retest du TILE à 4 ans d'intervalle (de 2,5 mois à 16 ans)
36 sujets avec NwC ou IH ou pseudohypersomnie:

Figure 2—MSLT-based diagnosis on repeat MSLT



PAS DE BIOMARQUEURS++

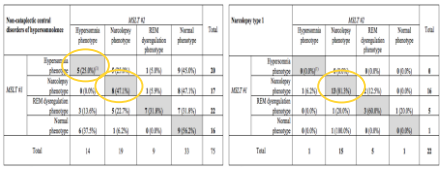
INSTABLE

Moyenne au 1° TILE: 5,5+- 3,7 et 7,3 +- 3,9 au second: Pas de corrélation (r=0,17, p=0,3)
Changement de diagnostic chez 53%: 42 % pour latence (>8 min) et 31% pour Soremps

ORIGINAL ARTICLE

Test–Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence

Two PSG-MSLTs in untreated patients with central hypersomnolence (median: 1.9 y)
22 NT1 and 75 others: NT2 (22.7%), IH (26.7%) or unspecified EDS (50.6%).



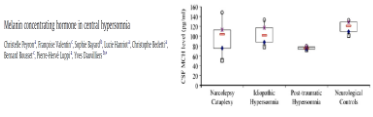
Instability of MSLT values: Change in classification in NT2 and IH / NT1
MSLT: To be perform twice to confirm the primary diagnosis of NT2 if stable criteria
BIOMARQUEURS à Découvrir pour diagnostic / sévérité / pronostic

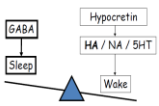
Neurobiology of NT2 ?

Pathology of lateral Hypothalamus ?

- Sleep-wake instability with high REM sleep propensity
  - Partial lesion of Hcrt neurons ? Increased activity of MCH neurons ?
- Circadian disturbances to explain the high REM sleep propensity

Is there a biological dysfunction?





No association between CSF MCH, histamine, and hypocretin levels in NT2

Cerebrospinal fluid monoamine levels in central disorders of hypersomnolence

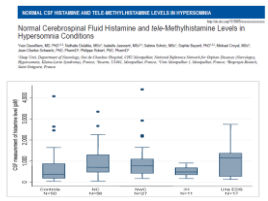
SLEEPJ, 2021, 1–9

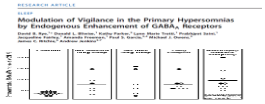
Lucie Barateau[1,2,3], Isabelle Jaussent[3,4], Julien Roeser[4], Claudio Ciardiello[4], Thomas S. Kilduff[5,*] and Yves Dauvilliers[1,2,3,*]

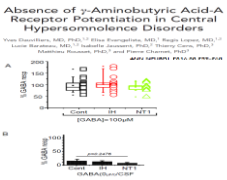
Neurobiology of IH ?

Deficiency in Waking system? No change in CSF hypocretin/ histamine levels

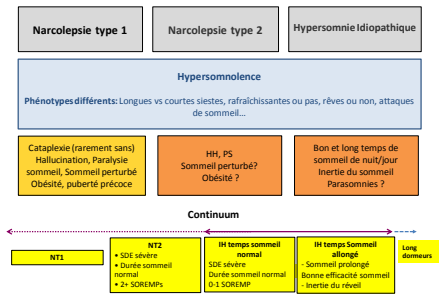
Excess in sleep system : GABA activity ?

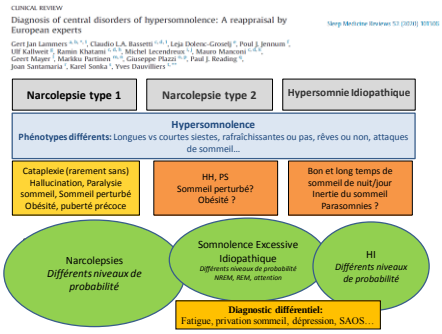






IH : Problem with phenotyping and its stability
Need to improve diagnostic criteria for IH
with similar assessment required between sleep centers





Hypersomnolences/ Narcolepsies dans les maladies neurologiques

- En rapport avec la pathologie*: Alzheimer, SEP, PK, TC, Steinert, lésion hypothalamique…*
  - Déficit en hypocrétine
  - Autres biomarqueurs: HA, MCH, DA, cytokines, amyloide ??
- En rapport avec le traitement
- En rapport avec un mauvais sommeil de nuit
- En rapport avec des troubles psychologiques associés
- En rapport avec des pathologies mixtes

Objectifs Thérapeutiques dans Narcolepsies (type 1 et 2)

- Réduire somnolence diurne excessive
- Contrôler les cataplexies, hallucinations, paralysies de sommeil
- Améliorer le sommeil de nuit
- Traitement des comorbidités: TCSP, SAOS, dépression, obesité
- Diminuer les conséquences psychosociales
  - Aide du patient et de la famille: Education thérapeutique
  - Association Patients: ANC
- Réévaluation des symptômes et du Handicap: Standardisation

PRIMER

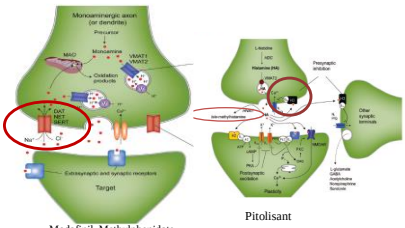

Narcolepsy

*Treatment of narcolepsy with or without cataplexy Solriamfetol

Prise en charge de Somnolence Diurne Excessive

- **Etiologique – Comorbidités**
  - Identifier les causes, comorbidités et les traiter
  - Privation de sommeil, apnées, poids, moral, iatrogénie…
- **Comportementale**
  - Hygiène de vie et de sommeil
    - siestes planifiées, courtes durées
    - Horaire de sommeil de nuit régulier
    - Activité physique
- **Médicamenteuse** pour les formes modérées/sévères
  - Traitement de la somnolence:
  - Traitements des symptômes associés: cataplexie, hallucination, paralysie, mauvais sommeil de nuit, surpoids

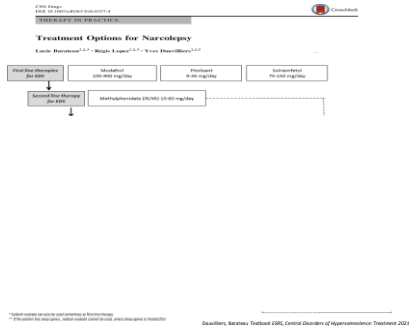
Psychostimulants: Mécanismes d'action



Modafinil, Methylphenidate, Solriamfetol…

Pitolisant

Mécanismes d'action: Dopaminergique, noradrénergique, histaminergique

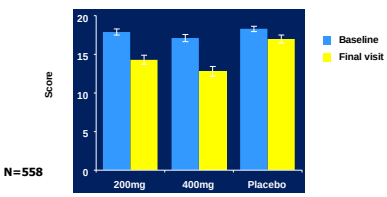


Modafinil (Modiodal ®): Inhibe DAT

- 100 à 400 mg/jour: Parfois 600 mg…
- Indications: Narcolepsie…
  - Arrêt récent des indications HI, SDE du SAOS sous PPC
- Effet éveillant – non excitant
- Peu ou pas de dépendance / tolérance
- Effets secondaires : céphalées, insomnie
  - ECG avant la prescription
- induction enzymatique (pilule ++)
  - Inhibe cytochrome cyp2c19 : induction
  - difficile en association aux anticoagulants, antiépileptiques
  - Majore les concentrations d'ISRS
- interdiction chez les sportifs

Narcolepsy 301 : Etude sur 9 sem Modafinil double aveugle contre placebo (200 and 400 mg)

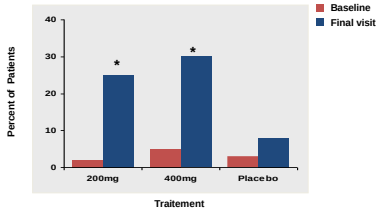
Echelle de SDE d'Epworth



N=558

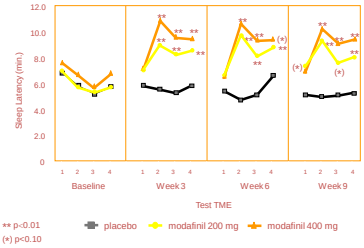
***p<0.001 (changement de baseline/ placebo)**

Narcolepsy 301 : % de Patients avec Epworth <10



*p<0.05 **(changement de baseline/ placebo)**

US 301 Modafinil Study
Test de maintien de l'éveil



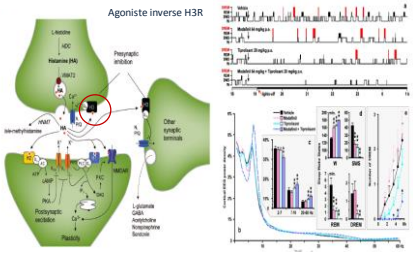
** p<0.01
(+) p<0.10

placebo modafinil 200 mg modafinil 400 mg

An inverse agonist of the histamine H_3 receptor improves wakefulness in narcolepsy: Studies in orexin$^{-/-}$ mice and patients

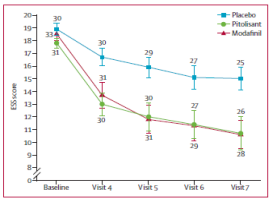
Jian-Sheng Lin,[a,b,*] Yves Dauvilliers,[c] Isabelle Arnulf,[d] Hélène Bastuji,[e] Christelle Anaclet,[a,b] Régis Parmentier,[a,b] Laurence Kocher,[f] Masashi Yanagisawa,[g] Philippe Lehert,[h] Xavier Ligneau,[i] David Perrin,[i] Philippe Robert,[i] Michel Roux,[i] Jeanne-Marie Lecomte,[i] and Jean-Charles Schwartz[i,j]

Agoniste inverse H3R

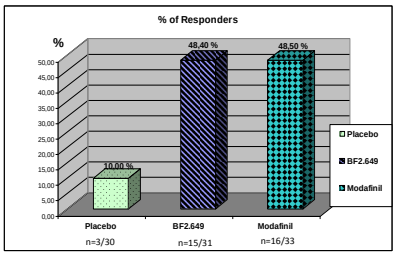


Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial

Yves Dauvilliers, Claudia Bassetti, Gert Jan Lammers, Isabelle Arnulf, Geert Mayer, Andrea Rodenbeck, Philippe Lehert, Claire-Li Ding, Jeanne-Marie Lecomte, Jean-Charles Schwartz, for the HARMONY I study group*

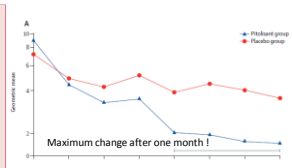


HARMONY I: Number of responders (ESS ≤ 10) at Day 56 : **WAKIX 36 mg**



Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial

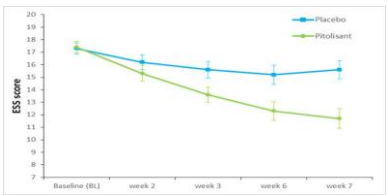
	Pitolisant group (n=54)	Placebo group (n=53)
Median age, years	34 (18-64)	39 (18-66)
Mean weight, kg	80·1 (17·8)	85 (18·1)
Mean height, cm	173·4 (9·1)	172 (10·7)
Mean body mass index, kg/m²	27·2 (5·2)	28·8 (6)
Men	26 (48%)	27 (51%)
Cataplexy episodes per week at prescreening	11 (8·9)	9·2 (8·8)
Mean sleep latency	4·2 (3·2)	4·7 (4·5)*
Mean ESS score at screening	17·3 (3·3)	17·1 (3·4)
History of associated symptoms		
Hallucinations	36 (67%)	32 (63%)
Ongoing hallucinations	32 (60%)	27 (53%)
Automatic behaviour	16 (30%)	14 (28%)
Ongoing automatic behaviour	13 (24%)	13 (26%)
Disturbed night sleep	37 (69%)	32 (63%)
Ongoing dyssomnia	33 (61%)	31 (61%)
Sleep paralysis	32 (59%)	32 (63%)
Ongoing sleep paralysis	24 (44%)	30 (59%)
Number of patients with at least one cataplexy medication in previous 3 months†	22 (41%)	41 (80%)
Number of patients continuing cataplexy medications during the trial	4 (7%)	8 (16%)
Mean BDI-13 item score at screening	5·3 (4·1)	5·3 (4·3)



WRC	Placebo [n=51]	Pitolisant [n=54]	ratio Rate and p
Baseline	7.31	9.15	rR(Pt/Pb), rR=0.512
Final	6.79	3.28	(95%CI = 0.435, 0.603, p <0.0001)

Improvement of narcolepsy symptoms … that persists at One Year
No additional safety concerns…

Daytime sleepiness significantly improved with pitolisant



ESS	Placebo (n=51)	Pitolisant (n=54)	Mean change difference and p
Baseline	17.3 + 3.2	17.4 + 3.3	-3.41 (95%CI -4.95, -1.87)
Final	15.4 + 5	12 + 5.4	p<0.0001

Responders using ESS
Final ≤ 10 and/or Δ ≥ 3
-Group with Pitolisant: 68,6%
-Group with placebo: 34%

Long-Term Evaluation of Safety and Efficacy of Pitolisant in Narcolepsy: Harmony 3 Study

Sleep 2019

102 patients inclus: 73 de novo / 29 previously treated
68 patients completed the 1-year study

Figure 1: Epworth Sleepiness Scale Scores Over Time

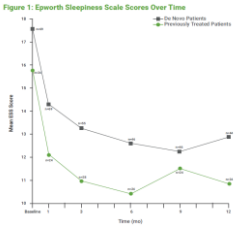
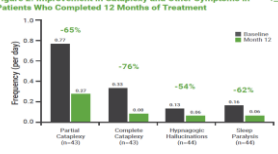


Table 3: Improvement in EDS, by Concomitant Medication

	Pitolisant 17.8 mg (n=43)	Pitolisant + Psychostimulants* (n=26)	Pitolisant + Antidepressants† (n=14)	Pitolisant + Psychostimulants* + Antidepressants† (n=13)
ESS score, mean (SD)				
Baseline	16.1 (3.7)	17.6 (3.4)	16.7 (2.9)	18.0 (4.3)
Change at Month 12 (LOCF)	-4.7 (5.3)	-5.2 (4.0)	-5.6 (4.6)	-4.0 (5.4)
Responders, Month 12 (LOCF), n (%)‡	26 (57.8)	13 (50.0)	8 (57.1)	10 (76.9)

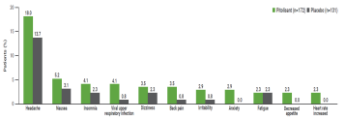
Figure 2: Improvement in Cataplexy and Other Symptoms in Patients Who Completed 12 Months of Treatment



Pitolisant safety: Most frequent adverse drug reactions

Adverse Event, n (%)	Pitolisant (n=172)	Placebo (n=131)
Any AE	85 (49.4)	54 (41.2)
Severe AE	16 (9.3)	3 (2.3)
Treatment-related AE	61 (35.5)	29 (22.1)
Serious AE	2 (1.2)	1 (0.8)
AE leading to discontinuation	6 (3.5)	5 (3.8)

No clinically relevant effects observed in vital signs or laboratory findings



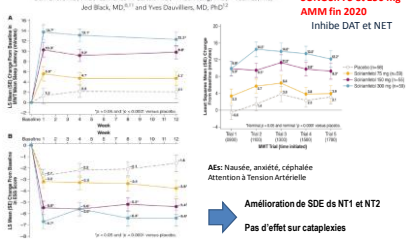
Most common AEs : headache and nausea

A Randomized Study of Solriamfetol for Excessive Sleepiness in Narcolepsy

ANN NEUROL 2019;85:359–370

Michael J. Thorpy, MB, ChB,[1] Colin Shapiro, MBBCh, PhD,[2] Geert Mayer, MD,[3] Bruce C. Corser, MD,[4] Helene Emsellem, MD,[5] Giuseppe Plazzi, MD,[6,7] Dan Chen, MD, PhD,[8] Lawrence P. Carter, PhD,[8,9] Hao Wang, PhD,[10] Yuan Lu, MS,[8] Jed Black, MD,[8,11] and Yves Dauvilliers, MD, PhD[12]

SUNOSI: 75 et 150 mg
AMM fin 2020
Inhibe DAT et NET

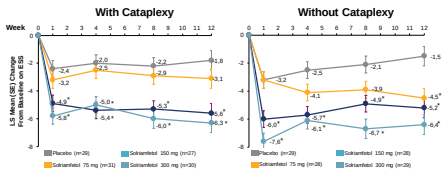


AEs: Nausée, anxiété, céphalée
Attention à Tension Artérielle

Amélioration de SDE ds NT1 et NT2

Pas d'effet sur cataplexies

Solriamfetol 150 mg and 300 mg decreased sleepiness in participants with and without cataplexy



*P<0.05 vs placebo.
ESS, Epworth Sleepiness Scale; LS, least squares; SE, standard error.

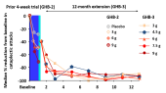
Effets secondaires des psychostimulants

- Modafinil: 100-400 mg en 2 prises
  - Céphalée, nausée, nervosité, insomnia, inducteur enzymatique++
- Pitolisant: 9-36 mg en une prise
  - Insomnie, céphalée, nausée, léger allongement QT
- Solriamfetol: 75-150 mg en une prise
  - Céphalée, nausée, nervosité, tension artérielle++
- Methylphenidate et surtout les Amphetamines
  - Céphalée, nausée, nervosité, insomnie
  - A fortes doses: **Effets cardiovasculaires**, réactions paranoides
- Peu ou pas d'addiction

SDE améliorée mais pas normalisée

Prise en charge des cataplexies

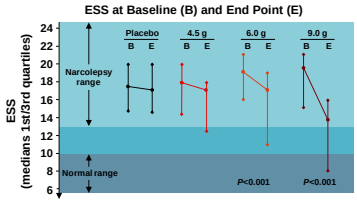
- **Comportementale**
  - Eviction des facteurs déclenchants
    - Rarement possible, souhaitable ?
- **Médicamenteuse** quand sévères
  - **Sodium oxybate**: 4,5g -9g en 2 prises la nuit
    - Attention au SAOS et à Dépression
  - **(Pitolisant)**
  - **Antidépresseurs**: Hors AMM
    - Venlafaxine, Clomipramine…
    - Effets secondaires: Poids, libido…
    - Rebond au sevrage +++
    "Risque d'Etat de Mal Cataplectique"
    - Rarement possible, souhaitable ?



- **Effets positifs sur cataplexies:**
  - Souvent efficaces aussi sur les hallucinations, paralysies…

Baisse du score d'Epworth

Sodium Oxybate: Etude contrôlée sur 8 sem



N=224 SXB-15
ESS = Epworth Sleepiness Scale.
Traitement stimulant maintenus Black J. 2004: Philadelphia

Effets secondaires

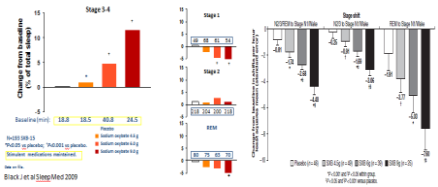
Sodium Oxybate: Etudes contrôlées sur 8 sem

	Incidence (%)				
		Sodium Oxybate (g)			
	Placebo	4.5	6.0	9.0	*P* Value
Nausée	3.3	11.8	15.9	27.3	0.002
Vertige	1.7	11.8	15.9	23.6	0.002
Somnolence	0.0	1.5	1.6	10.9	0.005
Enurésie	1.7	7.4	6.3	12.7	0.126
Trouble de l' attention	0.0	2.9	0.0	7.3	0.027
Douleur dorsal	1.7	0.0	6.3	0.0	0.035
Désorientation	0.0	1.5	0.0	7.3	0.013
Dyspnée	1.7	0.0	6.3	0.0	0.035
Crampes muscul	0.0	0.0	1.6	5.5	0.037
Contusion	0.0	0.0	0.0	5.5	0.011
Somnambulisme	0.0	0.0	0.0	5.5	0.011

Adverse events > 5% in any sodium oxybate group and whose incidence was dose-related (*P*<0.05), except enuresis.
SXB-15 N = 246 patients.
Data presented at the 2004 APSS meeting.

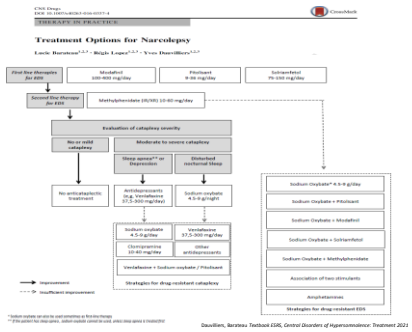
Prise en charge du mauvais sommeil de nuit

- **Hypnotiques type BZD, Z-drug: Peu efficace et Pas d'indication!**
- **Sodium Oxybate: Très efficace**

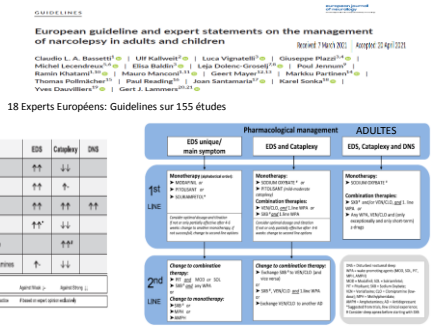


Black J et al Sleep Med 2009

Dauvilliers et al Sleep Med 2017



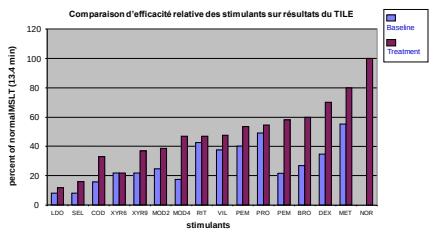
Dauvilliers, Barateau *Textbook ESRS, Central Disorders of Hypersomnolence: Treatment 2021*



18 Experts Européens: Guidelines sur 155 études

Drug	EDS	Cataplexy	DNS
Modafinil	↑↑	↓↓	
Pitolisant	↑↑	↑·	
Sodium Oxybate	↑↑	↑↑	↑↑
Solriamfetol	↑↑*	↓↓	
Venlafaxine / Clomipramine		↑↑*	
Methylphenidate / Amphetamines	↑·	↓↓	

Quelque-soit la médication, les narcoleptiques ont quasi- jamais un TILE normal



LDO: L-DOPA; SEL: selegeline; COD: codeine; XYR6: Xyrem 6.0g; XYR9: Xyrem 9.0g; MOD2: modafinil 200 mg; MOD4: modafinil 400 mg; RIT: ritanserin; VIL: viloxazine; PEM: pemoline; PRO: protryptiline; BRO: DEX: dexamphetamine; MET: metamine

Normal MSLT = 13,4 min chez sujets normaux

Adapted from MM Miller et al. *Sleep* 1994;17:352-371, by G Mayer.

Safety: Other Considerations

Agent	Additional Considerations
Modafinil/ (Armodafinil)[1,2,3]	• Reduce effectiveness of hormonal contraceptive agents • May increase heart rate and diastolic and systolic blood pressure • Allergic reactions and rashes
Solriamfetol[4,5,6]	• Precautions regarding blood pressure and heart rate increases • No effect on birth control
Pitolisant[2,7,8]	• May reduce effectiveness of hormonal contraceptives • No clinically relevant effects on vital signs, laboratory findings • May increase QTc intervals
SXB / LXB[9,10]	• High sodium formulation may be contraindicated in patients at risk for CVD events • May decrease body mass index • Common, early onset AEs are generally of short duration and decrease over time • LXB formulation may be ideal in those with CVD risks
Amphetamines / Methylphenidate[3]	• Schedule II controlled substance • High potential for abuse • Serious cardiovascular events (e.g., sudden deaths, stroke, myocardial infarction)

1. Volkow ND, et al. *JAMA*. 2009;301(11):1148-1154.; 2. Black JE, et al. *J Clin Sleep Med*. 2010;6(5):458-466.; 3. Drugs@FDA Website. 4. Meskill GJ, et al. *Sleep*. 2020;43(Suppl 1):A291.; 5. Zomorodi K, et al. *J Clin Pharmacol*. 2019;59(8):1120-1129.; 6. Carter LP, et al. *J Psychopharmacol*. 2018;32(12):1351-1361.; 7. Scarf-Grea C, et al. *Sleep*. 2019;42(Suppl 1):A244-245.; 8. Satmbi B, et al. *Sleep*. 2020;43(4):zsz252.; 9. Husain AM, et al. *J Clin Sleep Med*. 2020;16(9):1469-1474.; 10. Dauvilliers Y, et al. *Sleep*. 2020;43:A286.

Sleep disorders in neurology

French consensus. Management of patients with hypersomnia: Which strategy?

REVUE NEUROLOGIQUE 173 (2017) 8–18

R. Lopez [a,b,c], I. Arnulf [a,d,e], X. Drouot [f], M. Lecendreux [a,g], Y. Dauvilliers [a,b,c,*]

Table 1 – Interaction between narcolepsy treatments and its different comorbidities.

	Potential improvement	Potential aggravation
Obesity/Type 2 diabetes	Sodium oxybate Psychostimulants (except pitolisant)	Tricyclic antidepressants
Cardiovascular diseases	–	Psychostimulants (except pitolisant)
Mood andanxiety problems	Antidepressants (with moderate response)	Sodium oxybate Psychostimulants
Psychotic troubles	Aripiprazole	Psychostimulants (except pitolisant)
ADHD	Methylphenidate	–
Sleep apnea syndrome	–	Sodium oxybate
Restless legs syndrome/Periodic legs movements	–	Sodium oxybate Antidepressants
NREM and REM parasomnias	–	Sodium oxybate
Enuresis		
REM sleep behavior disorder	Sodium oxybate	Antidepressants

Decision-Making Strategies for Patients with Narcolepsy

- **In favor of MODAFINIL as first step:**
  - Moderate EDS
  - Mild cataplexy, if any
  - Low cardiovascular risk
  - Untreated SAS
- **In favor of PITOLISANT as first step:**
  - Moderate EDS and cataplexy
  - Presence of CVD
  - Untreated OSAS
  - Psychiatric problems
- **In favor of SXB / LXB as first step:**
  - Moderate EDS
  - Severe cataplexy
  - DNS, obesity (if no OSAS)
  - Able to comply with drug
  - LXB for comorbid CVD
- **In favor of SOLRIAMFETOL as first step:**
  - Resistant cases and severe EDS
  - Mild cataplexy, if any
  - Young female with oral contraception
  - Low cardiovascular risk
- **In favor of METHYLPHENIDATE / and finally AMPHETHAMINES:**
  - Resistant cases and severe EDS
  - Young female with oral contraception
  - Comorbid ADHD
  - Third line for amphetamines

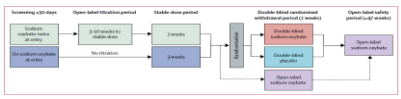
Personalized medicine ▶ Benefit/risk **ratio** needs to be assessed regularly ▶ Unmet needs in EDS remain

CME

Prise en Charge dans Conditions Particulières

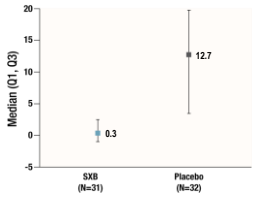
- **Patients réfractaires**
- **Enfants: Deux études:**
  - Xyrem finalisé: Acceptation aux US: bientôt EU officiellement
  - Pitolisant: En cours chez l'enfant
- **Grossesse: Contre indication des médicaments++ (Modiodal)**
- **Anesthésie**
- **Sujets Agés**
- **Prise en charge avec les années**
  - Beaucoup de Comédications ... Peu d'études

Treatment of paediatric narcolepsy with sodium oxybate: a double-blind, placebo-controlled, randomised-withdrawal multicentre study and open-label investigation



	Efficacy population		Enrolled population (N=106)
	Placebo (n=32)	Sodium oxybate (n=31)	
Age (years)			
Mean (SD)	11·8 (2·5)	11·6 (2·5)	11·9 (2·4)
Median (range)	12·0 (7–16)	12·0 (7–16)	12·0 (7–16)
Age group (years)			
7–11	14 (44%)	12 (39%)	38 (36%)
12–17	18 (56%)	19 (61%)	68 (64%)
Sex			
Male	17 (53%)	18 (58%)	63 (59%)
Female	15 (47%)	13 (42%)	43 (41%)
Sodium oxybate status at study entry			
Naive	19 (59%)	20 (65%)	74 (70%)
Taking sodium oxybate	13 (41%)	11 (35%)	32 (30%)
Previous sodium oxybate use (months)			
n	14*	11	33
Mean (SD)	19·93 (14·4)	24·64 (19·2)	18·2 (16·0)
Median (range)	12·5 (7·0–52·0)	15·0 (2·0–49·0)	12·0 (2·0–52·0)

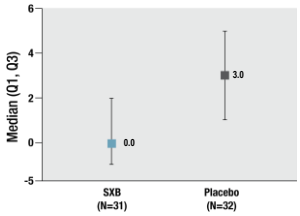
Changement sur la fréquence des cataplexies



P < 0.0001

Rank based ANCOVA with treatment and baseline cataplexy as a covariate;
Change in cataplexy from stable dose period to double-blind period; SXB, sodium oxybate

Changement sur Epworth CHAD



P = 0.0004

XYREM accepté aux USA et EU dans la narcolepsie chez l'enfant

Prise en Charge dans Conditions Particulières

- **Enfants: Xyrem (Approuvé par FDA/ et bientôt EU)**

- **Grossesse: Contre indication des médicaments++ (Modiodal)**
- **Anesthésie**
- **Sujets Agés**
- **Prise en charge avec les années**
  - Beaucoup de Comédications ... Peu d'études
- **Patients réfractaires**

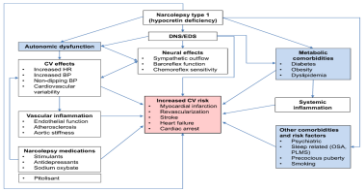
CLINICAL REVIEW

Cardiovascular disorders in narcolepsy: Review of associations and determinants

Sleep Medicine Reviews 58 (2021) 101440

Poul Jørgen Jennum [a,*], Giuseppe Plazzi [b,c], Alessandro Silvani [d], Lee A. Surkin [e], Yves Dauvilliers [f,g]

Medical comorbidities in NT1 include cardiovascular diseases
Relationships betwen NT1, hypertension, and cardiovascular risk: Complex and Unclear
Lack of nocturnal BP dipping, impact of DNS, Obesity, Diabetes, Depression



Can treatment for narcolepsy unbalance symptomatic benefits with cardiovascular safety ?

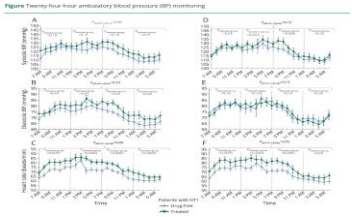
Effect of psychostimulants on blood pressure profile and endothelial function in narcolepsy

ABPM in 160 NT1 patients

Independant sample

68 untreated: 40% HTA
54 treated: 58% HTA

Increased 24h,day and night DBP and HR in the treated group



Dependant sample

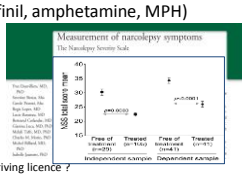
38 evaluated twice before /after medication

Increased 24h SBP and HR in treated group

Patients with NT1 treated with psychostimulants had higher BP and HR
At risk for CVD: Careful follow-up and specific management

Management of Narcolepsy in Sub-Populations

- **During Pregnancy ?** CI of all drugs (modafinil, amphetamine, MPH)



- **Long term management!**
  - Comedications often required
  - When to reassess patients in the sleep lab ?
    - For reevaluation of NT2 diagnosis
    - For MWT assessment for NT1/NT2: Every 5-year for driving licence ?
  - What to do in the outpatient clinic ? Every *6 months or 1 year*
    - Questionnaires: ESS, EQ5D, NSS for adults and children
    - Performances at School/ Professional….
    - Regular assessment of Depression, BMI, blood pressure

Measurement of Narcolepsy Symptoms in School-Aged Children and Adolescents

The Pediatric Narcolepsy Severity Scale

To validate the NSS in children: 14-item (15-item for adults)
209 patients from 6 to 17 y.o.
160 completed correctly the scale: 10-17 y.o., 68 untreated
65 patients completed it twice

NSS-P total score in the independent sample			NSS-P total score in the dependent sample		
Untreated patients N = 68	Treated patients N = 92		Untreated patients N = 33	Treated patients N = 33	
mean (SD)	mean (SD)	*p*	mean (SD)	mean (SD)	*p*
27.03 (8.23)	23.32 (10.13)	**0.02**	25.52 (8.81)	22.39 (8.82)	**0.03**

NSS-P was lower in treated than untreated patients
Minimal clinically important difference: 4 points
4 levels of severity defined from mild to very severe

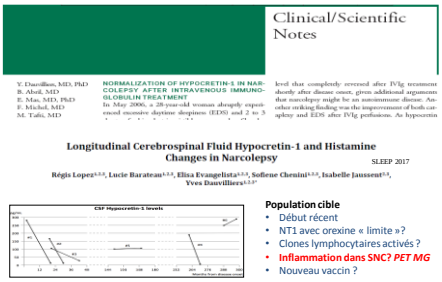
Valid NSS-P to assess symptoms frequency, severity and consequences in patients older than 10

NOUVEAUX TRAITEMENTS ?

Arrêt de destruction neuronale?

Immunothérapie

Immunothérapie: Quelle population? Quand? Quel Traitement?



Clinical/Scientific Notes

Y. Dauvilliers, MD, PhD
B. Abril, MD
E. Mas, MD, PhD
F. Michel, MD
M. Tafti, MD

NORMALIZATION OF HYPOCRETIN-1 IN NARCOLEPSY AFTER INTRAVENOUS IMMUNOGLOBULIN TREATMENT

In May 2006, a 28-year-old woman abruptly experienced excessive daytime sleepiness (EDS) and 2 to 3 [illegible] level that completely reversed after IVIg treatment shortly after disease onset, given additional arguments that narcolepsy might be an autoimmune disease. Another striking finding was the improvement of both cataplexy and EDS after IVIg perfusions. As hypocretin

Longitudinal Cerebrospinal Fluid Hypocretin-1 and Histamine Changes in Narcolepsy

SLEEP 2017

Régis Lopez[1,2,3], Lucie Barateau[1,2,3], Elisa Evangelista[1,2,3], Soflene Chenini[1,2,3], Isabelle Jaussent[2,3], Yves Dauvilliers[1,2,3]*

Population cible

- Début récent
- NT1 avec orexine « limite »?
- Clones lymphocytaires activés ?
- Inflammation dans SNC? *PET MG*
- Nouveau vaccin ?

Treatment with immune modulators in a child with recent-onset type 1 narcolepsy

Qidi Ding[1] · Fulong Xiao[1] · Xiaosong Dong[1] · Jun Zhang[2] · Fang Han[1]

CSF orexin-A levels after rituximab treatment in recent onset narcolepsy type 1

Pontus Wasling, MD, PhD, Clas Malmeström, MD, PhD, and Kaj Blennow, MD, PhD

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Neurol Neuroimmunol Neuroinflamm 2019;6:e613. doi:10.1212/NXI.0000000000000613

LETTER TO THE EDITOR

Treatment of narcolepsy with natalizumab

Thomas E. Scammell[1,*], Guo Luo[2], Priya Borker[1,3], Lee Sullivan[1], Kelsey Biddle[1,*] and Emmanuel Mignot[2]

Traitements dans Narcolepsie type 2 et Hypersomnie idiopathique

Narcolepsie Type 2: OUI

Symptomatique (SDE)

Modafinil, Pitolisant

Solriamfetol (NT1/2/SAS avec SDE)

FUTUR: Xyrem Mg …Xyrem LP ?? Agonistes recepteurs orexin

Hypersomnie idiopathique:
Pas de traitements en EU
Pas d'AMM/remboursés

Perspectives

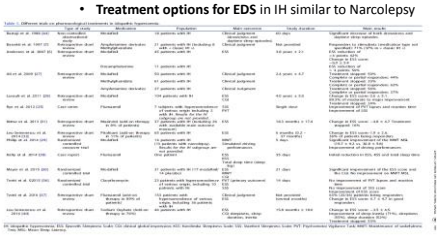
Symptomatique
(Hypersomnie et SDE)

Xyrem Mg: Etude JAZZ finalisée

Etude en cours:
Xyrem: avec PSG TME – CHU Montpellier

Treatment of Idiopathic Hypersomnia

- No approved drugs for the treatment of IH since 2021 (FDA)
- **Treatment options for EDS** in IH similar to Narcolepsy



Evangelista et al 2018

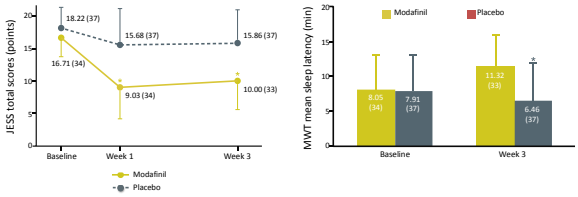
Inoue et al Sleep med 2021: RCT Modafinil: Effective and safe drug for EDS in IH without long sleep time

Overview of Pharmacological Trials in IH*

Treatment	Author	Patient population	Conclusion
Modafinil	Mayer et al. 2015	IH without long sleep time (n = 31)	Improvement on ESS: 6.0 points; on CGI: 1.0 point
Methylphenidate	Thakrar et al. 2018	IH (n = 9); NT1 (n = 70), NT2 (n = 47)	Improvement on ESS: 3.1 points
Dextroamphetamine	Ali et al. 2009	IH (n = 2)	0% complete or partial response
Sodium oxybate	Leu-Semenescu et al. 2016	Treatment-refractory IH (n = 46)	65% responders; improvement on ESS: 3.5 points
Pitolisant	Leu-Semenescu et al. 2014	Treatment-refractory IH (n = 65)	35% responders; improvement on ESS: 1.5 points
Mazindol	Nittur et al. 2013	Treatment-refractory IH (n = 37)	Improvement on ESS: 4.8 points
Flumazenil	Trotti et al. 2016	Refractory hypersomnolence (n = 153)	62.8% responders
Clarithromycin	Trotti et al. 2015	IH (n = 10); NT2 (n = 4); subjective hypersomnia (n = 6)	Improvement on ESS: 3.9 points
Transcranial direct current stimulation	Galbiati et al. 2016	IH (n = 8)	Improvement on ESS: 5.8 points

*These agents are not FDA-approved for the treatment of IH.
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders; ICSD = International Classification of Sleep Disorder
Schmelzhoek MS, et al. *Curr Sleep Medicine Rep.* 2019;5:207-214.; Evangelista E, et al. *Expert Opin Investig Drugs.* 2018;27(2):187-192.

Modafinil:† Efficacy in IH without Long Sleep Time



†Modafinil is not FDA-approved for the treatment of IH.
* p < .001
JESS = Japanese version of the Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test
Inoue Y, et al. *Sleep Med.* 2021;80:315-321.

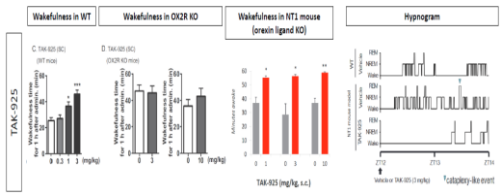
NOUVEAUX TRAITEMENTS DANS NT1 !

Arrêt de destruction neuronale?

Immunothérapie

Agoniste Hypocretinergique?

OX2R agonists: Perspective in NT1



OX2R selective agonist TAK925
- Improves waketime in WT and Orexin KO mice
- No change in OX2R KO mice
- Improves «NT1 symptoms» in orexin-ataxin3 mice

NOUVEAUX TRAITEMENTS DANS NT1 !

Arrêt de destruction neuronale?

Immunothérapie

Agoniste Hypocretinergique?

Symptomatique
(SDE- cataplexie…)

Pitolisant
Xyrem LP/ Mg
Modafinil-Anticonnexine
Solriamfetol (NT1/SAS avec SDE)

Optimiser Balance Bénéfice-Risque

Patient Reported Outcomes, Sécurité…
Médecine Personnalisée

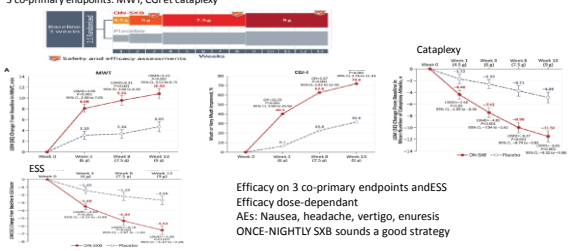
Once-nightly sodium oxybate (FT218) demonstrated improvement of symptoms in a phase 3 randomized clinical trial in patients with narcolepsy

SLEEP, 2021, 1–11

Clete A. Kushida[1,*], Colin M. Shapiro[2], Thomas Roth[3], Michael J. Thorpy[4], Bruce C. Corser[5], Akinyemi O. Ajayi[5], Russell Rosenberg[6], Asim Roy[6], David Seiden[5,6], Jordan Dubow[5] and Yves Dauvilliers[7,8,*]

Etude RCT REST-ON chez 212 patients (30% NT2): 107 ON-SXB vs 105 Placebo
3 co-primary endpoints: MWT, CGI et cataplexy

*FT-218 is not FDA/EMA-approved



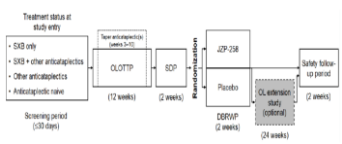
Efficacy on 3 co-primary endpoints andESS
Efficacy dose-dependant
AEs: Nausea, headache, vertigo, enuresis
ONCE-NIGHTLY SXB sounds a good strategy

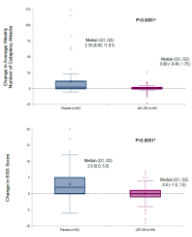
Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy

SLEEP, 2021, 1–13

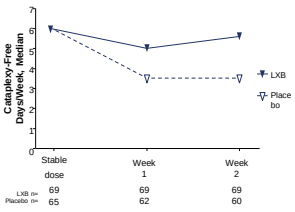
Richard K. Bogan[1,*], Michael J. Thorpy[2], Yves Dauvilliers[3,4], Markku Partinen[5], Rafael Del Rio Villegas[6,a], Nancy Foldvary-Schaefer[7], Roman Skowronski[8], Lihua Tang[9,†], Franck Skobieranda[9] and Karel Sonka[9,10]

202 patients enrolled
134 were randomized
Primary endpoint: changes in cataplexy/ week from end of RBRWP/SBP



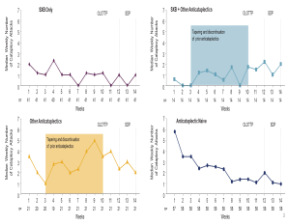


Median Cataplexy-Free Days per Week During DBRWP (Efficacy Population)[a]



DBRWP, double-blind randomised withdrawal period
[a]Defined as participants who took ≥1 dose of double-blind study drug and had ≥1 post-randomisation efficacy assessment.

LXB improved symptoms of cataplexy in the open phase



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Safety and efficacy of lower-sodium oxybate in adults with idiopathic hypersomnia: a phase 3, placebo-controlled, double-blind, randomised withdrawal study

Lancet Neurol 2022; 21: 53–65

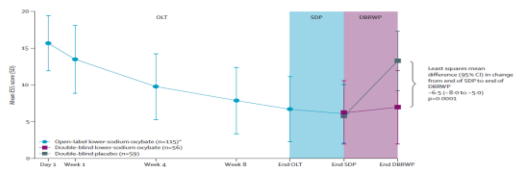
Yves Dauvilliers, Isabelle Arnulf, Nancy Foldvary-Schaefer, Anne Marie Morse, Karel Šonka, Michael J Thorpy, Emmanuel Mignot, Patricia Chandler, Rupa Parvataneni, Jed Black, Amanda Steckel, Dan Chen, Franck Skobieranda, Richard K Bogan

154 patients with IH included and 115 randomized with either PCB or LXB

ESS: primary endpoint

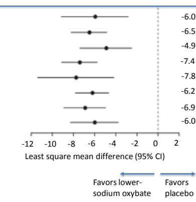
CGI and IHSS: Secondary endpoints

- Recall period: last week
- Time of administration: at every clinic visit



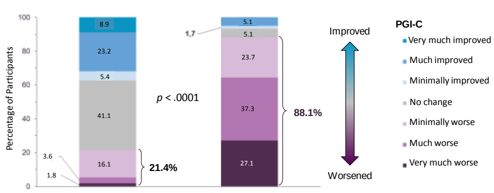
LXB: Efficacy in IH – Differences in ESS Scores Between Groups

	Placebo (n = 59)	Lower-sodium oxybate (n = 56)	Least squares mean difference (95% CI)	Nominal *p* value
Male	16	17	-6.0 (-9.2 to -2.8)	*p* = .0006
Female	43	39	-6.5 (-8.3 to -4.8)	*p* < .0001
Once nightly	11	15	-4.9 (-7.4 to -2.5)	*p* = .0004
Twice nightly	47	41	-7.4 (-9.2 to -5.7)	*p* < .0001
With long sleep	11	13	-7.8 (-11.4 to -4.2)	*p* = .0002
Without long sleep	48	43	-6.2 (-7.8 to -4.6)	*p* < .0001
Taking baseline IH medication	35	33	-6.9 (-8.9 to -4.9)	*p* < .0001
Treatment naïve	24	23	-6.0 (-8.3 to -3.7)	*p* < .0001



Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53-65.

LXB: Efficacy in IH – PGI-C

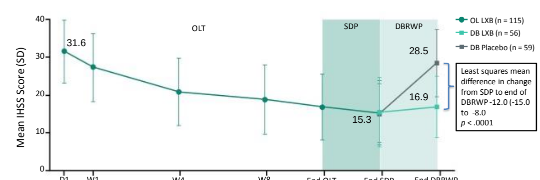


At the end of DBRWP, significant worsening in PGI-C ratings was observed in participants randomized to placebo vs. LXB (88.1% vs. 21.4% rated minimally/much/very much worse)

PGI-C = patient global impression of change

Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53-65.

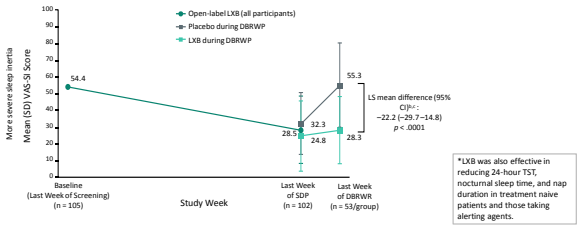
LXB: Efficacy in IH – IHSS



- Improvement in mean IHSS score from study entry to end of SDP
- Worsening in mean IHSS score from end of SDP to end of DBRWP with placebo; maintenance of improvement with LXB

Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53-65.

LXB: Efficacy in IH – Sleep Inertia and Total Sleep Time



*LXB was also effective in reducing 24-hour TST, nocturnal sleep time, and nap duration in treatment naive patients and those taking alerting agents.

Optimisation du SUIVI

Optimiser Balance Bénéfice-Risque

Efficacité, Sécurité…
Médecine Personnalisée

Mesures d'Efficacité

Clinique: Chaque 6 mois- 1 an

Interview clinique + Questionnaires

-ESS ….SF-36, EQ5D, BDI…

-Performances (Ecole/ Professionnel….) ?

-**Echelle spécifique: NSS et IHSS**

Neurophysiologique = **TME**: Chaque 5 ans ou changement de traitement

-Pour évaluer les risques (conduite), comorbidités

Mesures de Sécurité / Tolérance

Examen clinique: IMC, TA…

Risque de dépression

Risque cardiovasculaire: MAPA…

CONCLUSION - PERSPECTIVES

- Mieux comprendre l'Epidémiologie des Hypersomnolences "Stables"
- Mieux quantifier symptômes (Outils!!), Meilleur diagnostic !
- Diminuer le délai au diagnostic et le handicap personnel et sociétal
- Trouver des biomarqueurs - **OMIC** des Hypersomnolences centrales
- Mieux comprendre la cause de la mort des neurones à hypocrétine
- Envisager une **Médecine de Précision: Personnalisée - Préventive**

  avec un bon rapport Bénéfice-Risque

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