

Narcolepsy-101

Past, Present, Future

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Takeda Pharmaceuticals

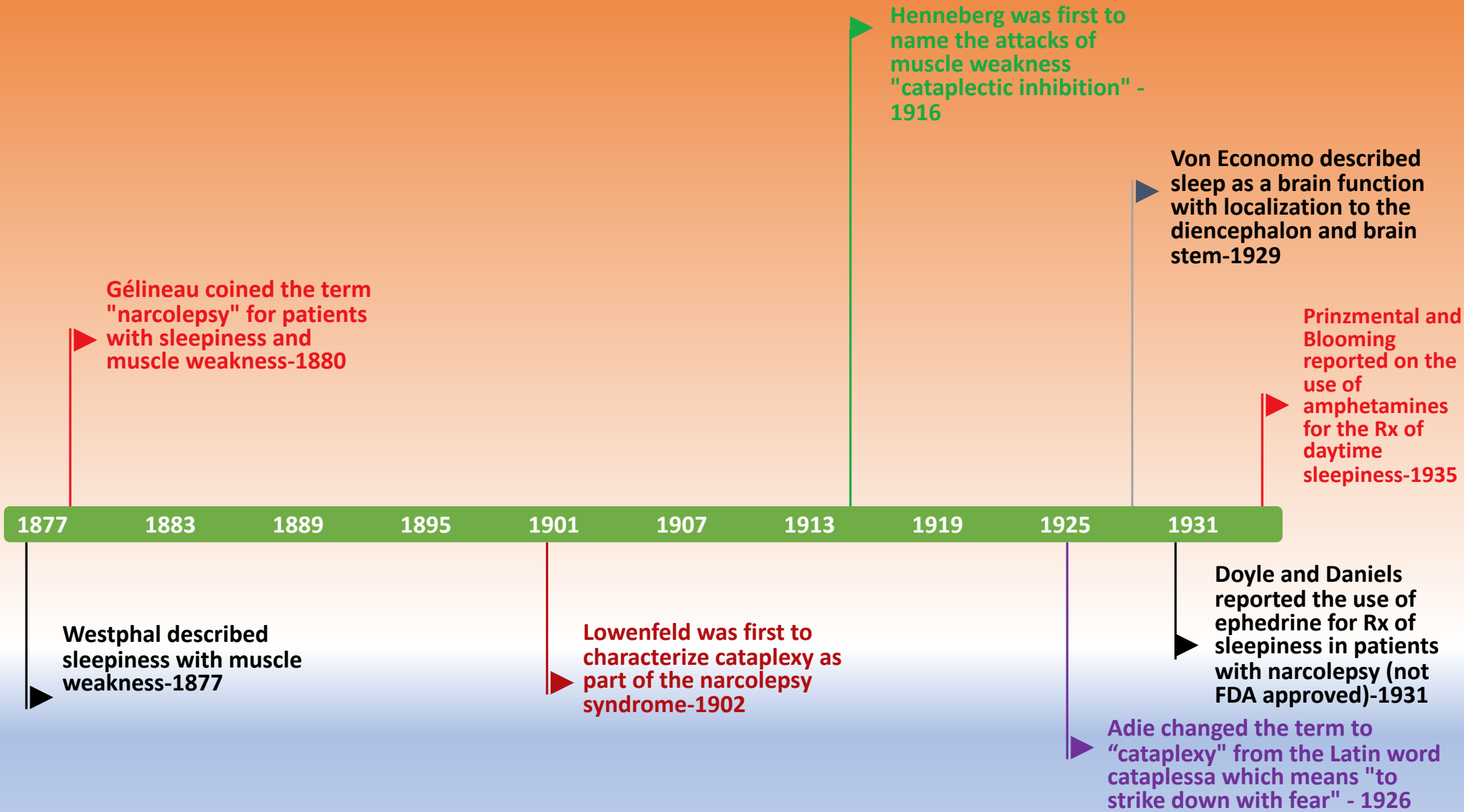
Diplomate, American Board of Sleep Medicine

Diplomate, American Board of Psychiatry and Neurology in Neurology and Sleep Medicine

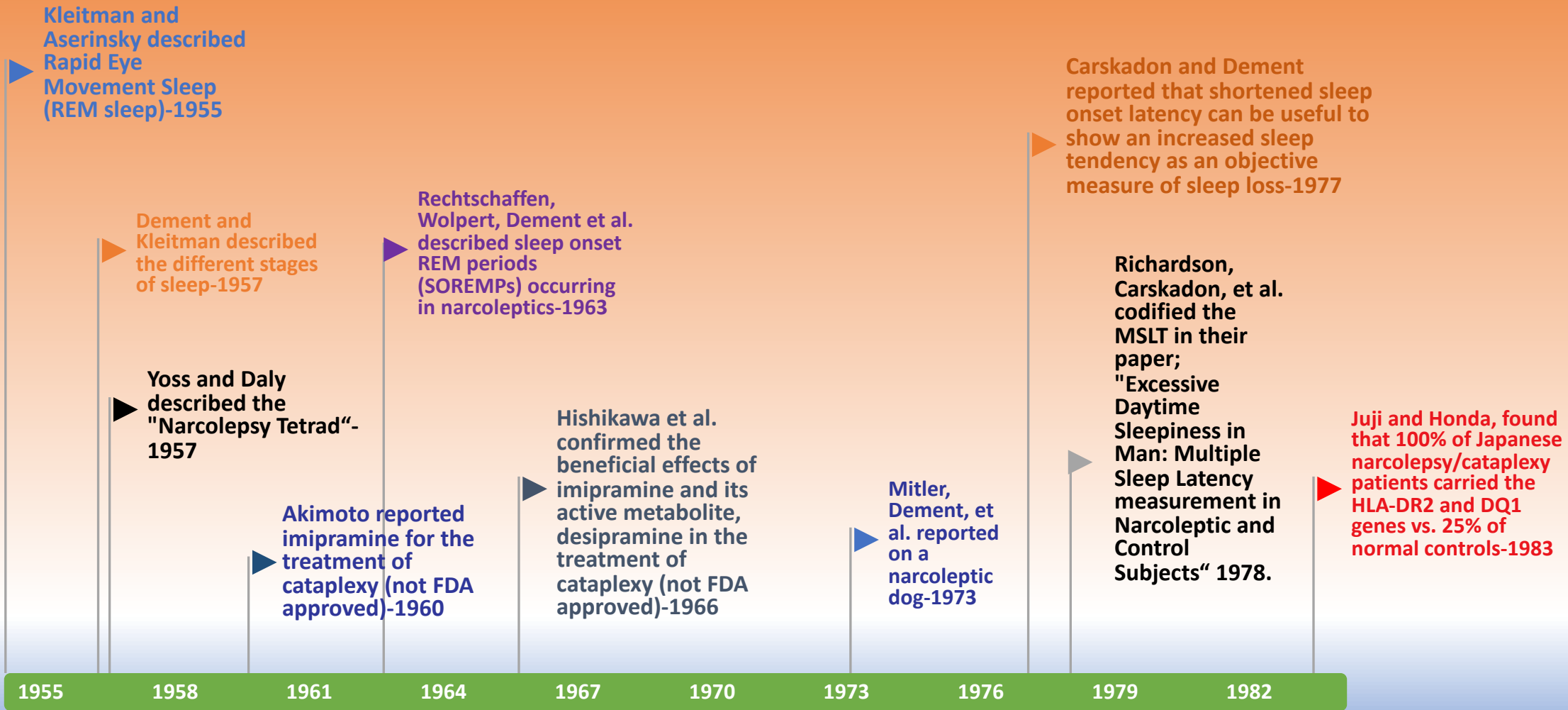
Conflicts of Interest*

- Currently, full-time employee of Takeda Pharmaceuticals-development of new drugs for narcolepsy
- Previously received research funds from
 - Jazz Pharmaceuticals
 - Avadel/Flamel
 - Harmony Biosciences
- Advisory Board Member
 - Jazz Pharmaceuticals
 - Avadel/Flamel
 - Aerial Pharmaceuticals

*This presentation reflects my personal views and opinions and does not necessarily reflect the position of Takeda Pharmaceuticals.



59 years



29 years

1998

de Lecea and Kilduff identified two peptides they named hypocretins (Hypocretin-1 and Hypocretin-2)-1998

Sakurai showed that the Hypocretins and Orexins were the same polypeptides-1998

Chemelli, Scammell, et al. reported narcolepsy/cataplexy-like traits in orexin knockout mice-1999

Nishino, Ripley, Overeem, Lammers and Mignot reported that there is a significant loss or complete absence of Hypocretin (orexin) in the brain/CSF in human narcolepsy-2000

Mignot showed canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene-1999

Modafinil (Provigil®) was approved by the FDA for excessive sleepiness in narcolepsy-1998

Sakurai, et al. identified two peptides they named Orexins (Orexin-A and Orexin-B)-1998

Sodium Oxybate (Xyrem®) was approved by the FDA to treat cataplexy associated with narcolepsy-2002

Sodium Oxybate (Xyrem®) was approved by the FDA to treat excessive daytime sleepiness and/or cataplexy associated with narcolepsy-2005

Armodafinil (Nuvigil®) was approved by the FDA for excessive daytime sleepiness associated with narcolepsy-2007

Dauvilliers, Montplaisir, Mignot, et al. described the association between post H1N1 infection and/or vaccination with the onset of Narcolepsy Cataplexy-2010

Dauvilliers, Bassetti, Lammers, et al. reported, pitolisant a selective histamine H3 receptor activator improved EDS compared to placebo and was well tolerated compared to modafinil in patients with narcolepsy-2013

Nagase et al. report the discovery of the first selective nonpeptide Orexin 2 receptor agonist

TAK 994 first oral OX2R agonist. Takeda Pharmaceuticals, 2019

Sunosi® (solriamfetol) and Wakix® (pitolisant) approved for EDS in narcolepsy, 2019

Black, Swick, Feldman, Doekel, Khayrallah, Brea and Ruoff reported ADX-N05 (JZP-110), a wake-promoting agent in a phase 2 trial, significantly improved objective and subjective symptoms of excessive daytime sleepiness in patients with narcolepsy-2014

TAK-925 OXR2 receptor agonist-IV formulation. Takeda Pharmaceuticals 2019

Narcolepsy Treatment Time Line

21 years

Narcolepsy

- **Lifelong neurologic/sleep disorder characterized by the disruption of the boundaries between sleep and wake states**
- **Classic pentad of signs and symptoms:**
 - **Excessive Daytime Sleepiness (EDS)**
 - **Cataplexy**
 - **Hypnagogic hallucinations**
 - **Sleep paralysis**
 - **Disrupted nighttime sleep (DNS) [nocturnal sleep fragmentation]**

Narcolepsy

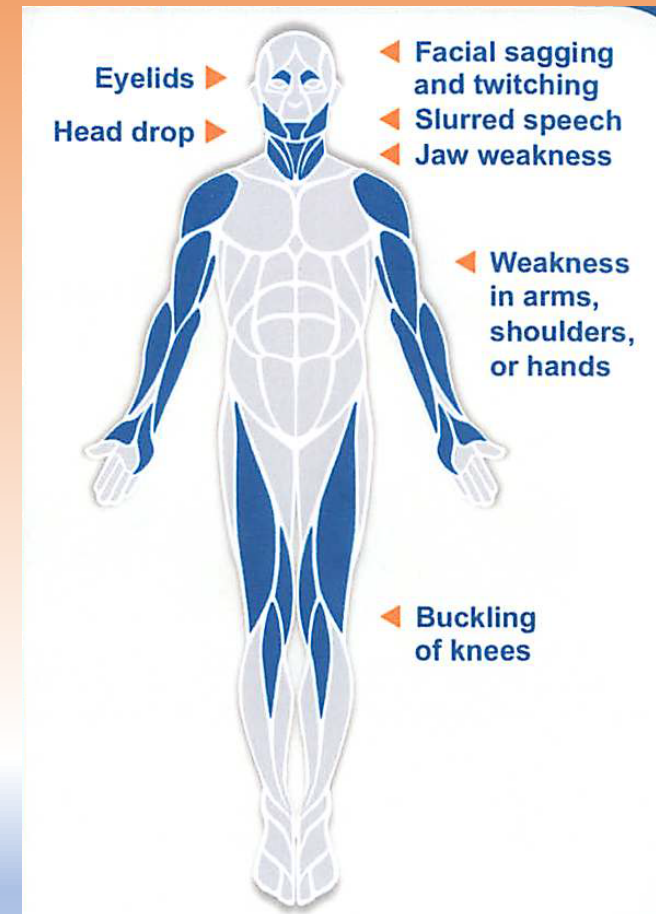
- **Ancillary symptoms:**
 - Automatic behavior
 - Loss of concentration and memory
 - Visual symptoms (blurred vision)
- **There are 2 distinct groups of patients with narcolepsy:**
 - Those with cataplexy (*Type 1 Narcolepsy as per ICSD-3 classification*)
 - Those without cataplexy (*Type 2 Narcolepsy as per ICSD-3 classification*)
- **Can coexist with other sleep disorders**
 - Obstructive Sleep Apnea
 - Restless Legs Syndrome
 - Periodic Limb Movements in Sleep
 - REM sleep behavior disorder
 - Nocturnal eating disorder

Narcolepsy

- **Sleepiness is usually the first symptom**
- **Commonly mistaken for:**
 - **Daydreaming**
 - **Insomnia**
 - **Drug Abuse**
 - **Depression/Bipolar disorder**
 - **Apathy**
 - **ADD**
 - **Seizures**

Cataplexy

- **Episodic weakness without altered consciousness lasting seconds to minutes and precipitated by excitement or emotion**
- **May occur several times/day or a few times/year**
- **Sagging of face, eyelid, or jaw; dysarthria (slurred speech-*particularly in children*); head drop; blurred vision; knee bucking; “drop attack”**
- **Can be unilateral**
- **Episodic blurring of vision**
- **Laughter is the most common trigger but can also be triggered by fright, excitement, fear, organism**
- **Usually develops within 3 years of EDS symptoms, but may develop 10-40 years later**



Sleep Paralysis

- **The inability to move for a few seconds or minutes during sleep onset or offset**
- **Often occurs in normal individuals on a relatively rare episodic basis but is far more common and almost universal in narcoleptics**
- **Paralysis ends spontaneously (fear reaction is most common) or after mild sensory/tactile stimulation**

Hypnagogic Hallucinations

- Vivid, “*waking dreams*” that occur during *transitions between* sleep and wakefulness
 - Hypnagogic (occurring at sleep onset)
 - Hypnopompic (occurring upon awakening)
- May accompany sleep paralysis or occur independently
- May be tactile or auditory
- Some awareness of surroundings is preserved
- Differentiated from dreaming during sleep

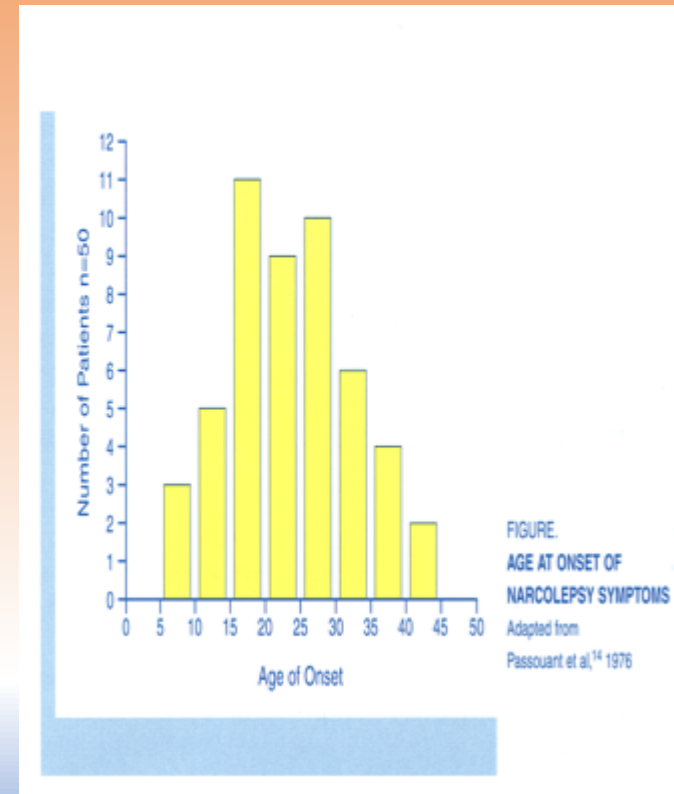
Disrupted Nocturnal Sleep (DNS)

- **Common aspect of narcolepsy that differs from DNS in other sleep disorders including insomnia**
- **Patients report:**
 - **Frequent arousals**
 - **Higher wakefulness after sleep onset (WASO)**
 - **Frequent shifts to wake or increased N1 sleep with reduction in N3 (SWS)**
 - **Decreased in overall sleep efficiency (SE)**
 - **Typically there is no prolongation of a return to sleep**
- **Several studies using PSG suggest that the decreased NREM and slow wave activity are possible mediators of the fragmented sleep**

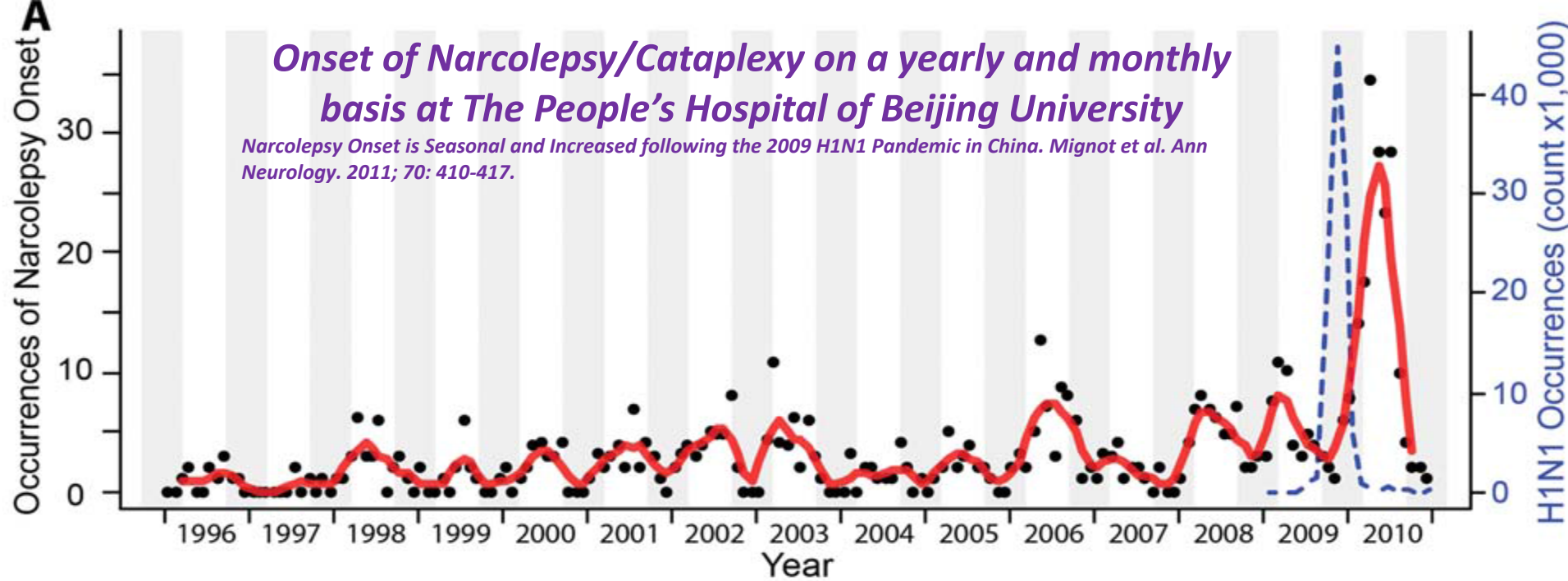
Narcolepsy-Age of Onset of Symptoms

- Onset between ages 15 and 30 in 60% of patients
- Age range from 5 to 63
- Median age of 22
- Onset of cataplexy ages 9 to 68
- Hypnagogic hallucinations ages 9 to 65
- Sleep Paralysis ages 10 to 58

- Age at onset of narcolepsy in two large populations of patients in France and Quebec. Dauvilliers Y, Montplaisir J, et al. *Neurology* 2001; 57:2029-2033.

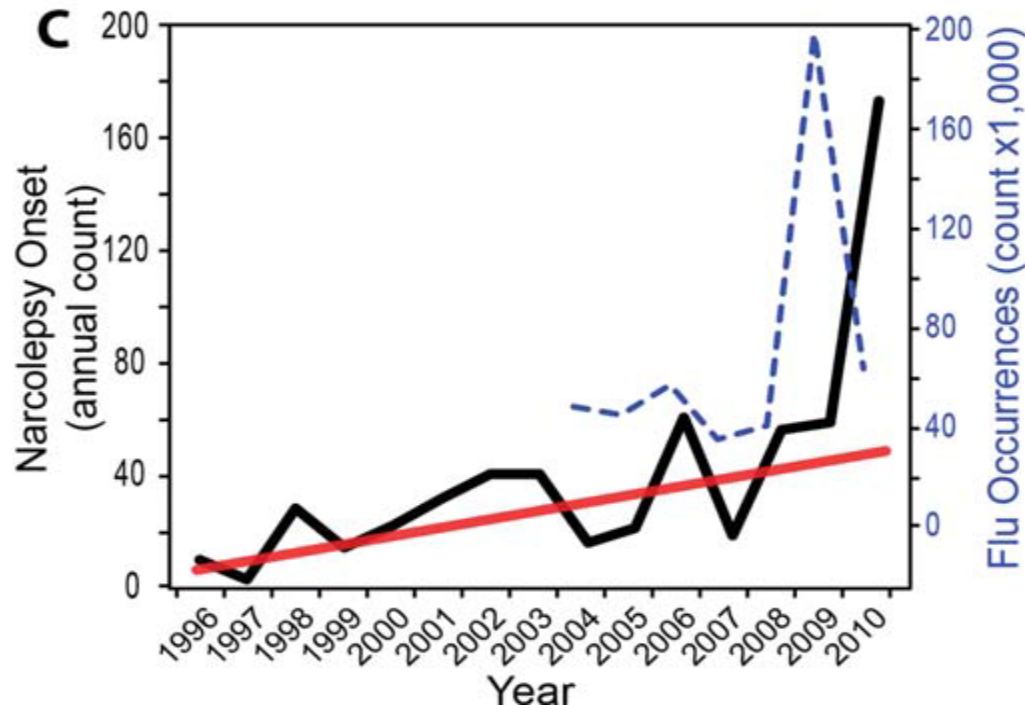
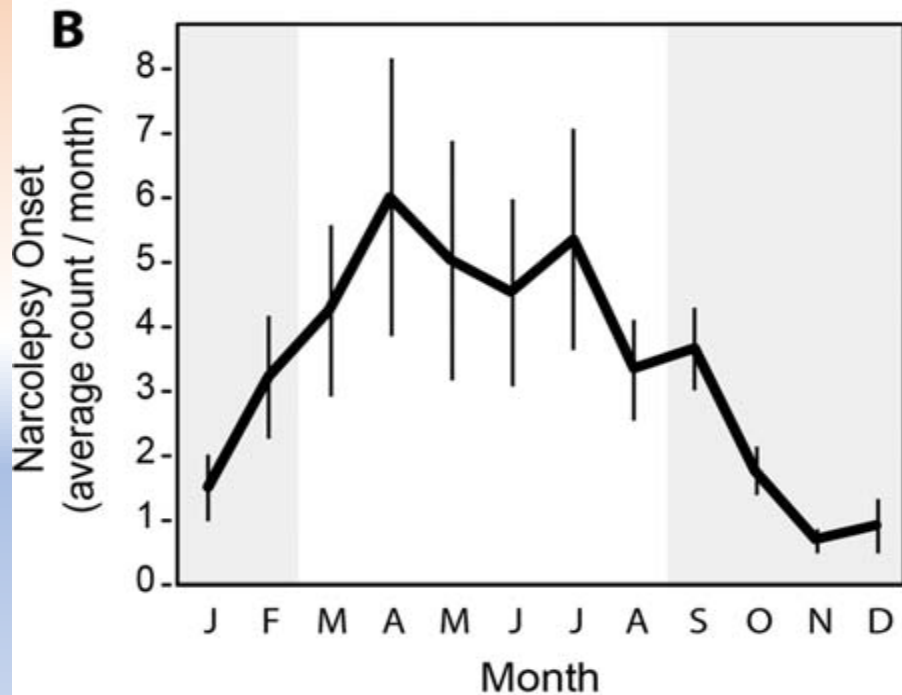


A) Monthly counts of narcolepsy-cataplexy onset over a 15 year period diagnosed at the People's Hospital, Beijing University



The number of yearly 2004-2010 influenza infections documented by government statistics is in blue

B) Mean of monthly occurrences



C) Yearly counts of narcolepsy onset

Widespread Underdiagnosis of Narcolepsy

- **Only 50,000 of the estimated 200,000 Americans with narcolepsy have been correctly diagnosed**
- **Almost as common as Multiple Sclerosis**
- **Can go 10 to 15 years after symptoms start before correct diagnosis is made**
- **A patient with narcolepsy/cataplexy sees an average of 5-7 physicians before a proper diagnosis is made**

• Delayed diagnosis of narcolepsy: characterization and impact. Thorpy and Krieger. Sleep Med 15 (2014) 502-507.

Narcolepsy and Immunity

- **Human leukocyte antigens (HLA) are strongly linked to many autoimmune diseases**
- **85% of patients with narcolepsy/cataplexy carry the genes for HLA DQB1*06:02**
- **<50% of patients with “atypical” or “mild” narcolepsy/cataplexy or those with narcolepsy without cataplexy have the gene for DQB1*06:02**
- **12-38% of the general population are HLA DQB1*06:02 positive (the test therefore is not useful as a general screening tool)**

Autoimmune Hypothesis

- **There is strong epidemiological evidence that susceptible individuals (defined as being HLA DQB1*06:02 positive) have a >100X greater chance of developing Narcolepsy/Cataplexy**
- **Narcolepsy/Cataplexy has been associated with**
 - **H1N1 infection and/or immunization**
 - **As a consequence of streptococcal infection**
 - **Specific antibodies hypothesized to attack hypocretin cells**

Elevated Tribbles homolog 2-specific antibody levels in narcolepsy patients. Cvetkovic-Lopes V, Bayer J, Dorsaz S, et al. J. Clin Investigation. Vol 120, 2010.

Autoimmune Hypothesis*

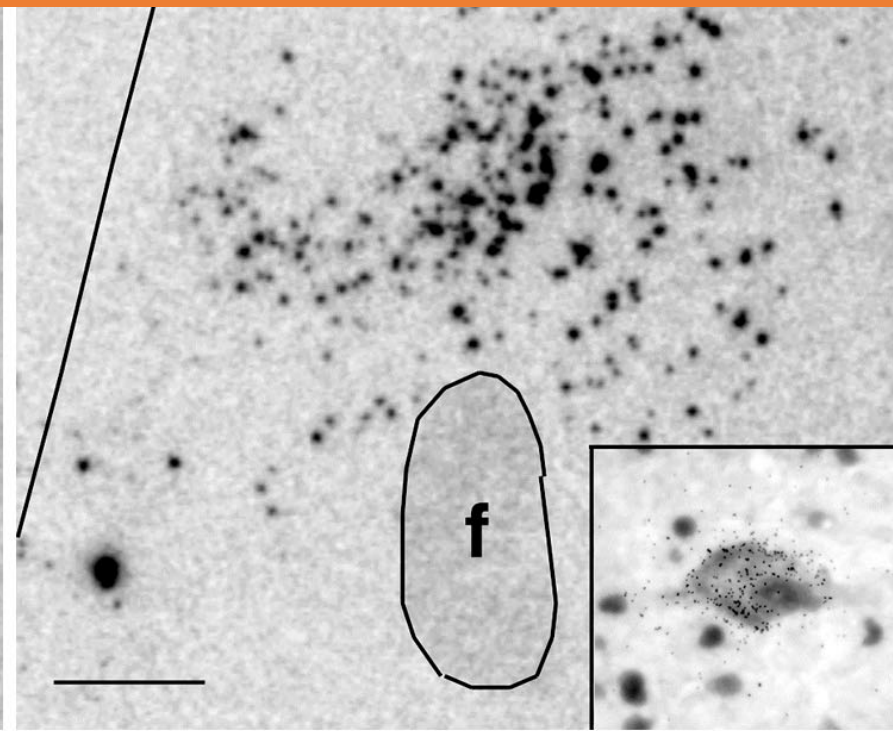
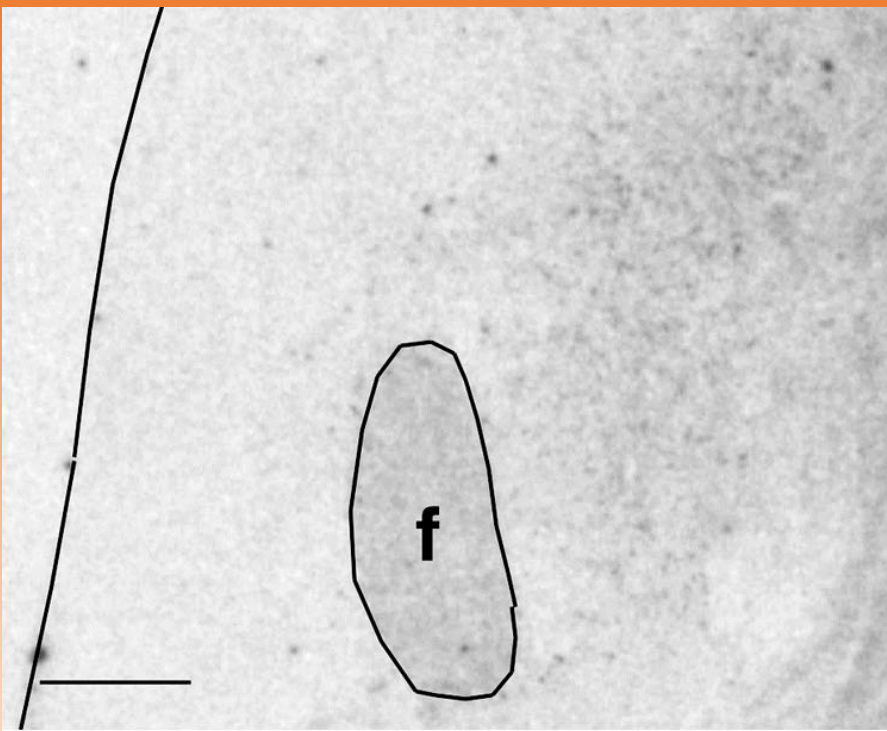
- **Multiple factors contribute to the development of autoimmune diseases**
 - **Genotype differences at the HLA level**
 - **HLA DQB1*06:01**
 - **Hormonal factors**
 - **Onset at or near puberty**
 - **Environmental factors**
 - **Associations with upper airway infections, strep infections, and influenza H1N1-infections and H1N1-vaccinations and by the strong seasonality of disease onset**

*The autoimmune basis of narcolepsy. Mahlios, De la Herran-Arita, and Mignot. *Curr Opin Neurology*; 2013; 23; 767-773.

Hypocretins (Orexins)

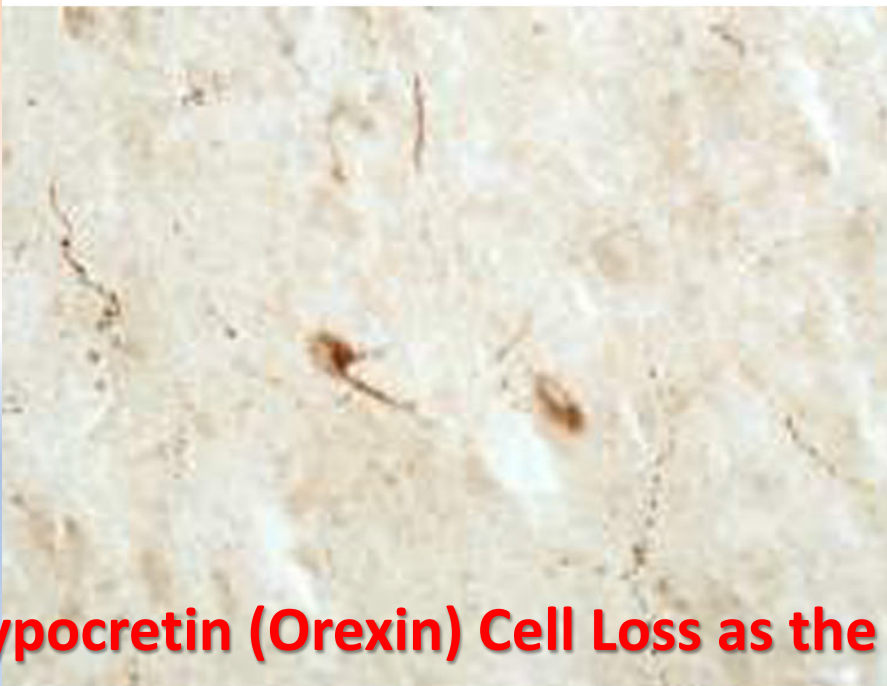
- **Human narcolepsy/cataplexy is caused by loss of hypocretin (orexin) neurons in the dorsolateral hypothalamus (70,000 neurons in a paired set)**
- **Thought to be caused by an autoimmune process directed specifically against hypocretin neurons in the hypothalamus (not by a mutated gene)**
 - **The *canine form* (e.g., Doberman Pinchers) of narcolepsy is caused by a single mutated hypocretin receptor 2 gene in an autosomal recessive pattern**

Hcrt loss as
the cause of
narcolepsy



Normal
hypothalamus

Abnormal
structure
and severe
loss of
Hcrt
peptide
staining



Normal
Hcrt
peptide
staining

Hypocretin (Orexin) Cell Loss as the cause of narcolepsy vs. normal tissue

Measuring Sleepiness

- **Subjective scales**
 - **Stanford Sleepiness Scale**
 - **Epworth Sleepiness Scale**
- **Objective Testing**
 - **Polysomnography/Multiple Sleep Latency Testing (PSG/MSLT)**
 - **Maintenance of Wakefulness Test (MWT)**

Objective Tests Used to Diagnose Narcolepsy

- **Polysomnogram (PSG)**
 - Measures a variety of signals during sleep using electrodes placed on the scalp
 - Test measures the electrical activity of the brain (electroencephalogram) and heart EKG (electrocardiogram) and the movement of muscles EMG (electromyogram) and eyes EOG (electrooculogram)
 - Also monitors breathing
- **Multiple sleep latency test (MSLT)**
 - Measures how long it takes patients to fall asleep during the day
 - Patients asked to take four or five naps, each nap two hours apart
 - Observe sleep patterns
- **Hypocretin test (just became clinically available through Mayo Clinic)**
 - Levels of hypocretin in CSF (spinal fluid)
 - levels <110 pg/ml are considered significant for the diagnosis of narcolepsy
 - One clinical laboratory approved to do the test

Classification of Narcolepsy

- DSM-V (American Psychiatric Association-2013)
 - Narcolepsy [with cataplexy]
 - Recurrent periods of irrepressible need to sleep, lapsing into sleep or napping occurring within the same day; occurring 3X per week over the past 3 months
 - Presence of at least one of the following
 - Episodes of cataplexy (occurring at least a few times/month)
 - Hypocretin deficiency (CSF containing ≤ 110 pg/ml)
 - PSG showing an initial SOREMP period ≤ 15 minutes or an MSLT with ≥ 2 SOREMPs and a mean SOL ≤ 8 minutes
 - *Note: the PSG/MSLT may not be necessary under this classification if there is "documented cataplexy"*
 - Narcolepsy without cataplexy but with hypocretin deficiency
 - Narcolepsy with cataplexy but without hypocretin deficiency (<5% of narcolepsy cases)
 - Autosomal dominant narcolepsy, obesity, and type 2 diabetes (low CSF Hcrt-1 levels)

Classification of Narcolepsy

- **ICSD-3 (American Academy of Sleep Medicine-2014)**
 - **Narcolepsy Type 1 [Narcolepsy with Cataplexy]**
 - Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥ 3 months
 - Cataplexy and a mean SOL of ≤ 8 min and ≥ 2 SOREMPs on an MSLT (a SOREMP on the preceding night's PSG can substitute for one of the SOREMPs on the MSLT)
 - OR
 - CSF HYPOCRETIN-1 concentration of ≤ 110 pg/mL

Classification of Narcolepsy

- **ICSD-3 (American Academy of Sleep Medicine-2014)**
 - **Narcolepsy Type 2 [Narcolepsy without Cataplexy] (All criteria must be met)**
 - Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥ 3 months
 - Mean SOL ≤ 8 min and ≥ 2 SOREMPs (a SOREMP on the preceding PSG can count as one SOREMP for the MSLT)
 - Cataplexy is absent
 - CSF has NOT been measured or is >110 pg/mL
 - The hypersomnia is not better explained by another sleep disorder, medical, psychiatric or neurological disorder

Classification of Narcolepsy

- **ICSD-3 (American Academy of Sleep Medicine-2014)**
 - **Idiopathic Hypersomnia**
 - Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥3 months
 - Cataplexy is absent
 - MSLT shows <2 SOREMPs or no SOREMPs if there was a SOREMP on the preceding night's PSG
 - MSLT demonstrates a mean SOL=≤8 minutes
 - Documented long sleep times (≥660 minutes) per 24 hours
 - Insufficient sleep time is ruled out

Goals of Treatment

- **Reduce daytime sleepiness**
- **Reduce/eliminate cataplexy**
- **Control ancillary symptoms**
 - **Nightmares and unpleasant frequent dreams**
 - **Hallucinations**
 - **Sleep paralysis**
 - **Disturbed nocturnal sleep**
- **Improve cognitive, psychosocial and work functioning**
- **Improve safety of patient and public**

Behavioral Treatment

- **Naps**
 - 20 min naps 2 or 3 per day (when possible)
 - Avoid driving when sleepy
 - Avoid high carbohydrate foods
- **Maintain good sleep hygiene (try NOT to deviate from routine sleep/wake schedules)**
- **Cataplexy**
 - Avoid emotional situations likely to induce cataplexy
- **Psychosocial support**
 - Family
 - School
 - Job
 - Education
 - Narcolepsy Network
 - Wake Up Narcolepsy
 - National Sleep Foundation

Pharmacologic Narcolepsy Management

- **Treatment of excessive daytime sleepiness (EDS)**
 - Stimulants (methylphenidate, amphetamines)
 - modafinil (Provigil®)-racemic mixture of “r” and “s” forms of modafinil*
 - armodafinil (Nuvigil®)-pure “r” isomer of modafinil*
 - solriamfetol (Sunosi®)-a novel wake-promoting compound is a selective norepinephrine/dopamine reuptake inhibitor (SNDRI)*
 - pitolisant (Wakix®)-H3 (histamine inverse receptor agonist (increases release of histamine as a wake-promoting neurotransmitter))*
- **Treatment of Cataplexy (none are FDA approved for this indication)**
 - Tricyclic antidepressants (TCAs)
 - Selective Serotonin Reuptake Inhibitors (SSRIs)
 - Selective Serotonin Noradrenergic Reuptake Inhibitors (SSNRIs)
- **Both EDS and Cataplexy**
 - Sodium Oxybate (Xyrem®)*

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Benefits and Limitations of Current Treatment

- “Wake Up Narcolepsy” survey of patients [2013-2014] (n= 2017; data were analyzed of 1697 respondents along with information from their direct care givers)
 - 62% were between the ages of 25-54
 - 78% had narcolepsy symptoms for >3 years (prior to diagnosis)
 - 59% had cataplexy
- “Improved” EDS with FDA approved medications: 85.4%
 - 42.3% had improved cognition
 - 51.8% improved fatigue
- Despite treatment most patients continue to struggle with daily symptoms
 - Residual EDS symptoms in 64.8%
 - Constant fatigue 37.4%
 - Cognitive impairment 40.8%
- Cognitive symptoms are very common and are under-appreciated by clinicians

New Agents Under Research/Development

- **Non-hypocretin-based therapies**
 - Once nightly sodium oxybate “micropump sodium oxybate” Avadel/Flamel Technologies
 - **Low-sodium oxybate**
 - **GABA-A receptor agonists (IH)**
 - flumazenil
 - clarithromycin

Other Agents Under Research/Development

- **Hypocretin/Orexin-based therapy**
 - **Hypocretin/Orexin-1 peptide**
 - *Intra-cerebro-ventricular administration* has been shown to increase arousal and reduce cataplexy in narcoleptic mice
 - *Intranasal administration of Hcrt-1* (limited human trials showed no effect on wakefulness but there were changes in REM sleep parameters)
 - **Non-peptide selective Hypocretin/Orexin-2 Receptor agonists**
 - TAK-925 (IV infusion) has been shown to increase wakefulness in narcoleptic mice, sleep deprived healthy human subjects and patients with Type 1 Narcolepsy and reduction in cataplexy-type behavior in narcolepsy knockout mice (TAK 925)*
 - TAK 994 is administered as an oral formulation and is now under investigation in a phase 1 study in healthy volunteers**, ***

*Evans R, Hazel J, Faessel H, et al., Results of a Phase 1, 4-Period Crossover, Placebo Controlled, Randomized, Single Dose Study to evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK 925, a novel Orexin 2 Receptor Agonist, in Sleep-Deprived, Healthy Adults, Utilizing Modafinil as an Active Comparator. Poster presentation, World Sleep 2019, Vancouver, BC, September 2019.

**Ishikawa T, Suzuki M, Kajita Y, et al., Discovery of a novel, orally available orexin 2 receptor-selective agonist, TAK-994, as a therapeutic drug for narcolepsy. Poster presentation, World Sleep 2019, Vancouver, BC, September 2019.

***Kimura H, Ishikawa T, Suzuki M. A novel, orally available orexin 2 receptor-selective agonist, TAK-994, ameliorates narcolepsy-like symptoms in narcolepsy mouse models. Poster, World Sleep 2019, Vancouver, BC, September 2019.

Limitations of Treatment

- No current approved agent returns the patient back to a “normal” state and as most medications there are reported adverse reactions:
 - modafinil (Provigil[®])/armodafinil (Nuvigil[®]) - (headache, palpitations, hypertension, anxiety)*
 - solriamfetol (Sunosi[®])-headache, nausea, decreased appetite, anxiety and insomnia are the most common adverse reactions (incidence $\geq 5\%$)*
 - Pitolisant (Wakix[®])- headache, insomnia, náusea, anxiety, increase in HR*

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