

NARCOLEPSY

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The Five Musketeers

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Background on Narcolepsy

Narcolepsy is a chronic, neurologic disorder that affects the brain's control of the sleep-wake cycle. It is likely to be caused by the defect of parts of the hypothalamus and it can appear at any age, most commonly begins in adolescence. 1 in 2000 people are affected and majorly underdiagnosed.

A normal sleep cycle includes 4 stages. A person with narcolepsy may skip the first few cycles, then go into REM, or possibly go directly into REM, which is what causes a person to collapse. REM is the stage of sleep where a person experiences dreams, and when a narcoleptic experiences REM while they are wide awake, it results in half-sleep dreams and temporary paralysis.

Types of Narcolepsy

Type 1 (narcolepsy with cataplexy): involves individual reports of cataplexy, or determined by low levels of hypocretin.

Type 2 (narcolepsy without cataplexy): individual does not report any signs of cataplexy.

- **Cataplexy:** a sudden muscle weakness in the face, neck, and legs in response to strong emotions.

Secondary Narcolepsy: results from an injury to the hypothalamus.

Symptoms

- Excessive daytime sleepiness (EDS): Also known as sleep attacks. It is a persistent background feeling of sleepiness with a tendency to doze off at intervals throughout the day, often at inappropriate times.
- Hypnologic hallucinations: vivid, often frightening sensory hallucinations while falling asleep. These could be caused by the blend of wakefulness and the dreaming that takes place with REM sleep.
- Cataplexy: a sudden muscle weakness in the face, neck, and knees in response to strong emotions (surprise or anger). Some people have only mild weakness, such as head or jaw drop, but some people completely collapse to the ground.

Causes (1)

- Many cases of narcolepsy are thought to be caused by a lack of the brain chemical hypocretin, which regulates sleep.
- Immune system problems: When antibodies mistakenly attack healthy cells and tissue, it's known as an autoimmune response. Scientists discovered that some people with narcolepsy produce antibodies against a protein called trib 2. Trib 2 is produced by an area the hypothalamus of the brain, which also produces hypocretin. This results in a lack of hypocretin, which means the brain is less able to regulate sleep cycles.

Causes (2)

- A number of factors may increase a person's risk of narcolepsy: hormonal changes (puberty or menopause), major psychological stress, change in sleep patterns, infection (Swine flu) or having the vaccine Pandemrix.
- Narcolepsy can sometimes happen as a result of an underlying condition that damages the areas of the brain that produce hypocretin (head injury, brain tumor, multiple sclerosis)

Possible Genes Involved

- HLA-DQB1
- Part of the HLA family of genes, Human Leukocyte Antigen complex. In other species, more commonly known as major histocompatibility complex (MHC).
- HLA proteins help the immune system differentiate between foreign proteins and body's own proteins.
- HLA-DQB1 is a gene responsible for a protein that attaches to the protein produced from HLA-DQA1 functional protein complex called an antigen-binding DQ $\alpha\beta$ heterodimer. This protein complex presents foreign peptides to the immune system triggering an immune response. Variations of the HLA genes provides room for many possible variations to a wide range of foreign peptides.

Possible Genetic Causes of Narcolepsy

- Increase risk of developing narcolepsy is increased by a version of the *HLA-DQB1* gene called *HLA-DQB1*06:02*.
- Unclear as to why this specific gene variation causes elevated risk. Increase evidence that malfunction of immune system is related to narcolepsy.
- Speculation of a link between the loss of the hypocretin producing neurons in the hypothalamus being triggered by the abnormality of the immune system, although no direct evidence.
- Many HLA variations found in people with narcolepsy are common in the general population so it's pretty unclear of the exact genetic causes. Other genetic and epigenetic factors could be at play as most cases of narcolepsy are sporadic.

HLA-DBQ1 Gene

Some info about HLA-DBQ1 from gene cards:

<http://www.genecards.org/cgi-bin/carddisp.pl?gene=HLA-DQB1&keywords=HLA-DBQ1>

Diagnosis

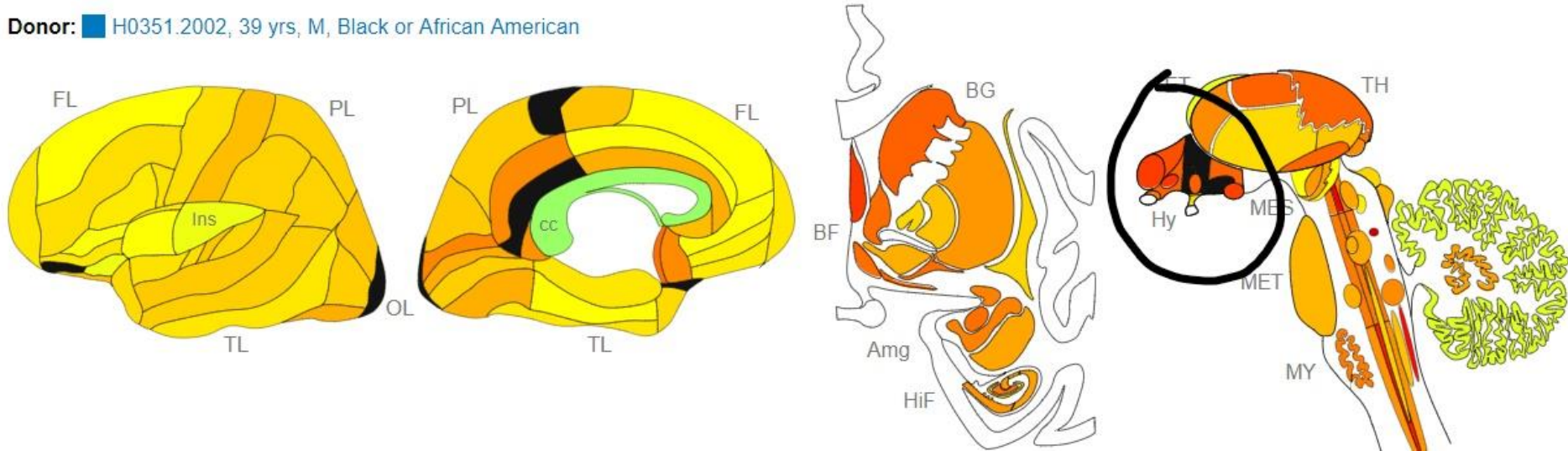
Polysomnogram (PSG): overnight recording of brain/muscle activity, breathing and eye movements.

Multiple Sleep Latency Test (MSLT): patients take multiple naps per day, with doctors recording time it took to fall asleep and elapsed time until REM.

Biopsy: spinal tap to measure hypocretin-1 levels.

Hypocretin Receptor 1

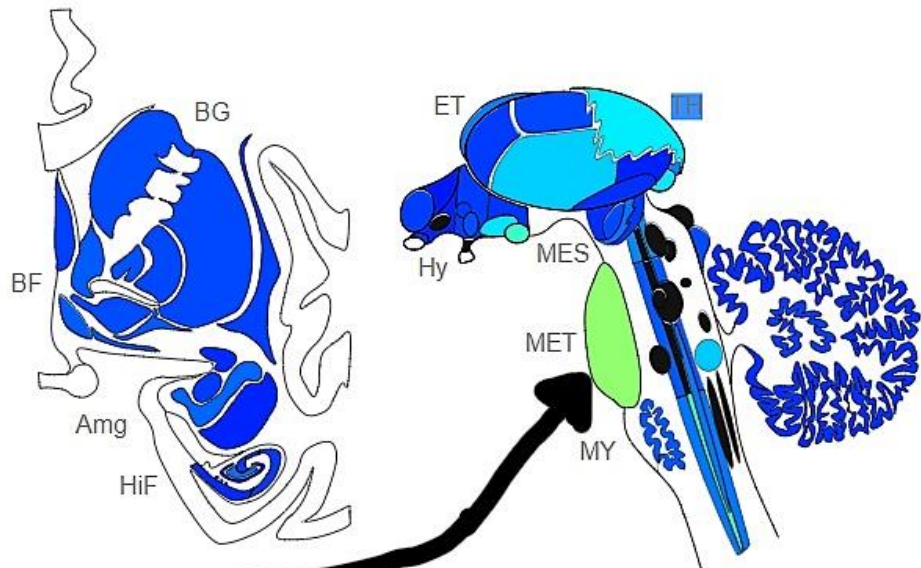
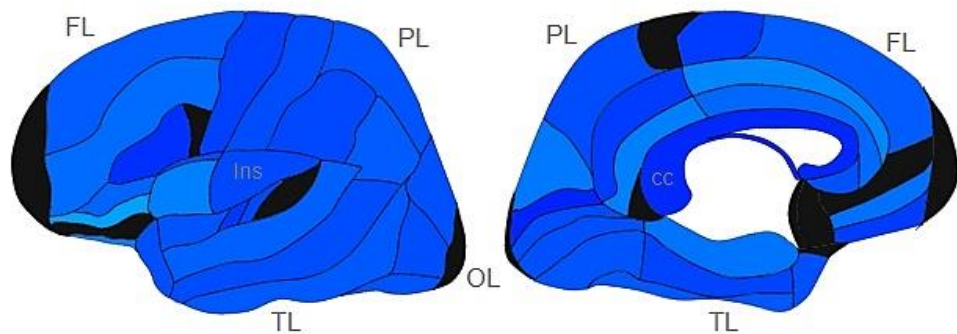
Donor: ■ H0351.2002, 39 yrs, M, Black or African American



<http://human.brain-map.org/microarray/gene/show/3044>

Hypocretin receptor 2

Donor: ■ H0351.1009, 57 yrs, M, White or Caucasian



Structure: pontine nuclei, **z-score:** 3.48882, **log2 level:** 5.16334

<http://human.brain-map.org/microarray/gene/show/3045>

Current Treatments

- No cure
- Armodafinil (*Nuvigil*); Modafinil (*Provigil*); Amphetamines (*Desoxyn*)
- SSRIs- block reuptake of 5-HT
- *Pitolisant*- selective inverse agonist of histamine H3 autoreceptor
- Exogenous melatonin
- Treatments mostly aim to increase amount of monoamines in synaptic cleft

Current Treatment-Xyrem (sodium oxybate)

- Helps 2 common symptoms
 - Excessive daytime sleepiness (EDS)
 - Cataplexy
- Studied for more than 20 years.
 - Clinical trial results available.
 - Approved by the FDA in 2002.
- Mechanism of action unknown.
 - Known metabolite of GABA
- Issues with Xyrem
 - FDA classifies it as a Schedule III substance, with illicit use given Schedule I violations.
 - Abused for its euphoric and calming effects.

Issues with Xyrem



About
Narcolepsy

About
XYREM

Getting
XYREM

Taking
XYREM

Support &
Savings

For Healthcare
Providers



Important Safety Information

WARNING: This medicine can have very serious side effects and has been misused and abused. Do not use with other medicines that slow your breathing or mental activity, or cause sleepiness.

XYREM has caused changes in alertness (or consciousness) and trouble breathing (respiratory depression). Call your doctor right away if you have any of these serious side effects. These effects happened even when XYREM was given in recommended doses. In studies, almost all of the patients with narcolepsy who were given XYREM were also taking medicines to help them stay awake during the day.

XYREM is a form of gamma hydroxybutyrate (GHB). Abuse of GHB alone or with other drugs that cause changes in alertness (or consciousness) has caused serious side effects. These effects include seizures, trouble breathing (respiratory depression), very low levels of alertness (or consciousness), coma, and death.

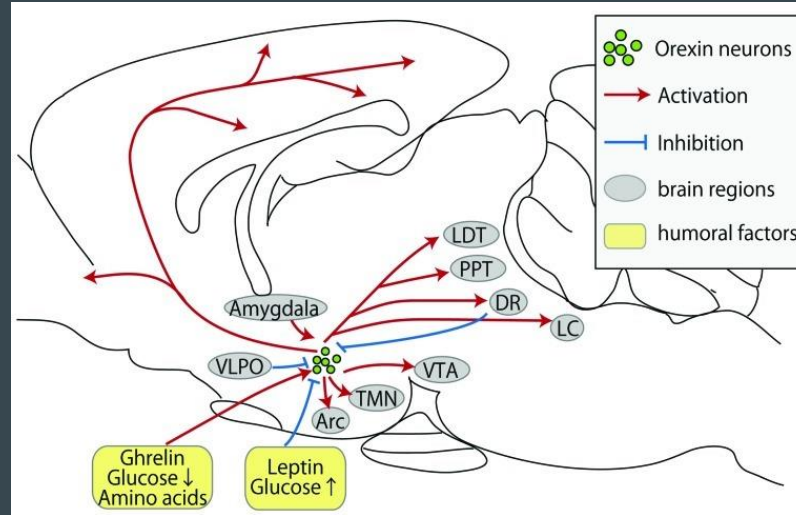
Because of these risks, you have to go through the XYREM REMS Program to have your prescription for XYREM filled. The XYREM REMS Program uses the central Certified Pharmacy. For further information, go to www.XYREMREMS.com or call 1-866-XYREM88[®] (1-866-997-3688). Both patients and their doctors have to join this Program.

Novel Treatment - Solfriametol (JZP-110)

- Significant novel treatment - potential for FDA approval late 2018
 - Phase III trials completed in Jan 2018
 - FDA accepted Jazz Pharmaceuticals' NDA for market approval in March 2018
- Phenylalanine-derived norepinephrine and dopamine reuptake inhibitor
 - Does not target serotonin reuptake or monoamine oxidases (MAOs)
 - Reduced abuse potential vs. stimulants

Solfriametol

- Treats excessive daytime sleepiness by promoting wakefulness
 - Clinical trials showed improvement on various wakefulness tests
 - Dopamine promotes wakefulness (i.e. amphetamines) and can reduce melatonin
 - Norepinephrine also promotes arousal; associated with hypocretin-induced wakefulness
 - Hypocretin-producing neurons project to monoaminergic regions important for arousal



Possible Future Treatments

- Blocking adenosine receptors in VLPO
- Increase activity of locus coeruleus (normally active in waking)
- Blocking alpha-2 adrenergic receptors in LC

VIDEOS



Cataplexy Attack



What Narcolepsy looks like

References

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<https://www.drugbank.ca/drugs/DB09072>

<https://clinicaltrials.gov/ct2/show/NCT00066170?term=xyrem&cond=narcolepsy&draw=2&rank=2>