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Development Program for Pitolisant in Patients with Myotonic Dystrophy

Analyst Event
June 17, 2021

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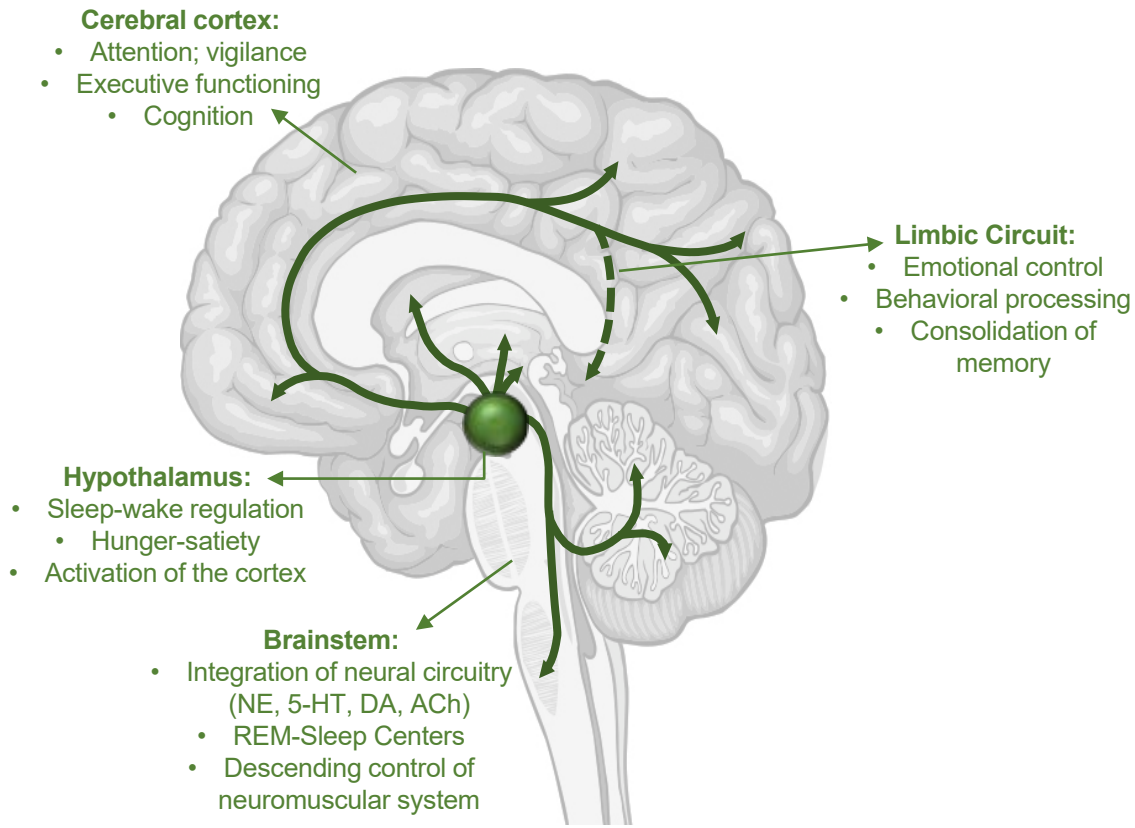
Topics to be Covered

- Life cycle management (LCM) strategy for pitolisant
- Overview of Myotonic Dystrophy (DM)
- Patient insights
- Scientific rationale for investigating pitolisant in patients with DM
- Phase 2 clinical trial of pitolisant in patients with DM1
- Concluding remarks

Pitolisant: *Portfolio in a Product* Opportunity

Mechanism-based approach to drug development and initial LCM studies based on:

- Role of histamine in normal physiologic functioning
- Role of histamine in disorders of orexin deficiency
- Location of H_3 receptors throughout the CNS
- Limited H_3 receptor populations outside the CNS
- Proven clinical efficacy of pitolisant for EDS



Pitolisant has a unique MOA with potential for multiple additional indications in rare disease patient populations with unmet medical needs

Life Cycle Management for Pitolisant

"Portfolio in a Product"
Evolving Beyond Sleep & Wakefulness

Label Expansion in Narcolepsy

Building industry leadership in narcolepsy

- Pediatric Narcolepsy indication
- Pediatric Exclusivity

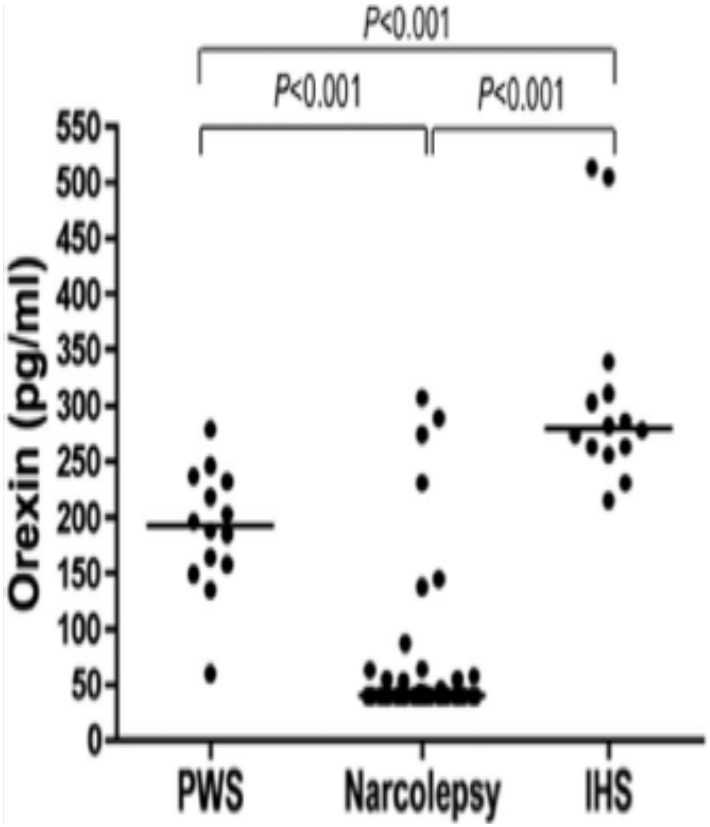
New Indications Based on H_3R MOA in Additional Rare Disease Patient Populations

Excessive daytime sleepiness (EDS) primary endpoint and exploring new clinical endpoints related to attention/vigilance, cognitive function, behavior and fatigue

- Prader-Willi Syndrome (PWS)
- Myotonic Dystrophy (DM)

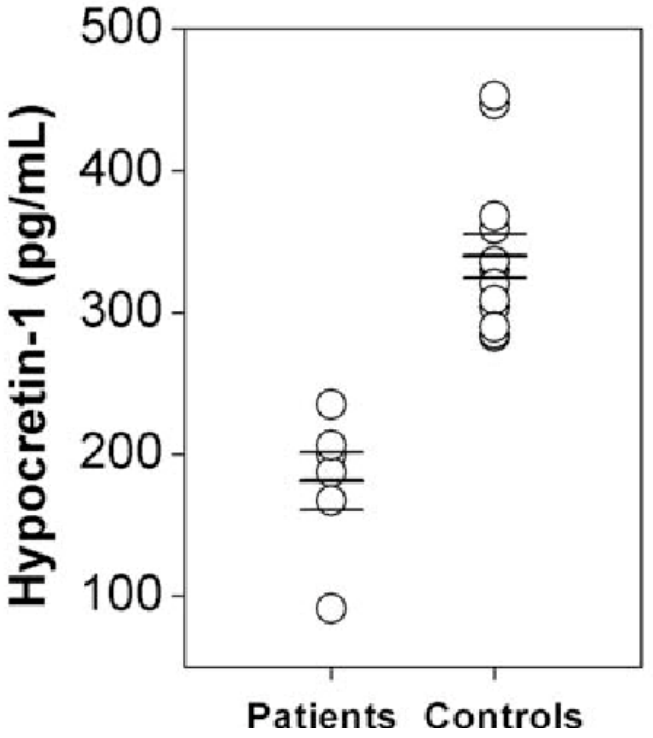
Common Thread in Disorders Being Investigated: Decreased Orexin Levels

Decreased Orexin in PWS



Omokawa M, et al. Decline of CSF orexin (hypocretin) levels in Prader–Willi syndrome. Am J Med Genet; 2016:1181–1186.

Decreased Orexin in DM1

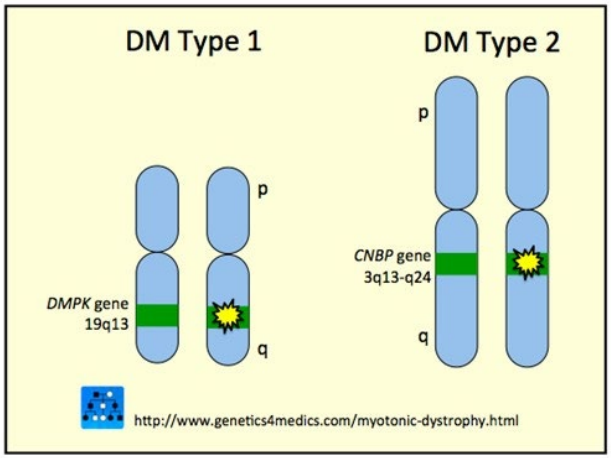


Martinez-Rodriguez J, et al. Decreased hypocretin-1 (Orexin-A) levels in the cerebrospinal fluid of patients with myotonic dystrophy and excessive daytime sleepiness. Sleep; 2003 May 1;26(3):287-90.

Evidence of hypothalamic dysfunction and impaired orexin system; important role of histamine in setting of orexin deficiency

Myotonic Dystrophy: Disease Background

- Rare, neurological and multi-system disease
  - *Dystrophia Myotonica (DM)*
- Most common form of adult-onset muscular dystrophy
- Genetic disorder, autosomal dominant inheritance; two types:
  - DM1 trinucleotide repeats (CTG) in DMPK gene on Chromosome 19
  - DM2 tetranucleotide repeats (CCTG) in CNBP gene on Chromosome 3

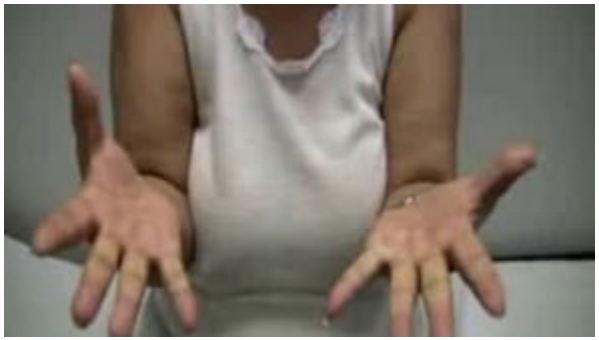


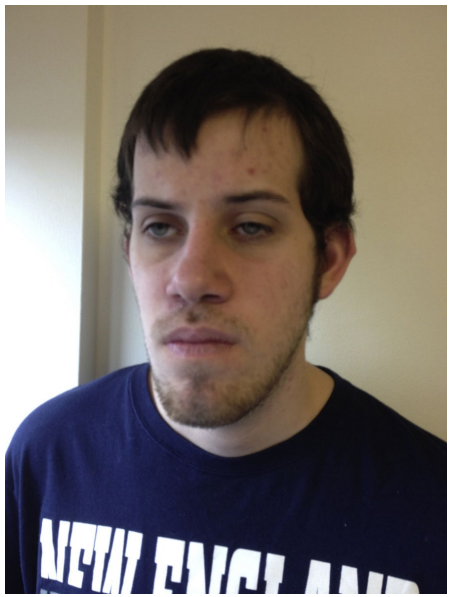
- Epidemiology
  - DM1 much more common than DM2
  - Estimated prevalence from medical literature ~1:8000[1,2]
  - Latest epidemiologic data from newborn screening study[3]
    - Prevalence of genetic mutation 1:2100 births
    - Suggests ~160,000 people in the US with the genetic defect for DM1
  - Estimated number of patients currently diagnosed: 40,000
    - Potential for increased diagnosis with more awareness of the disorder and its impact

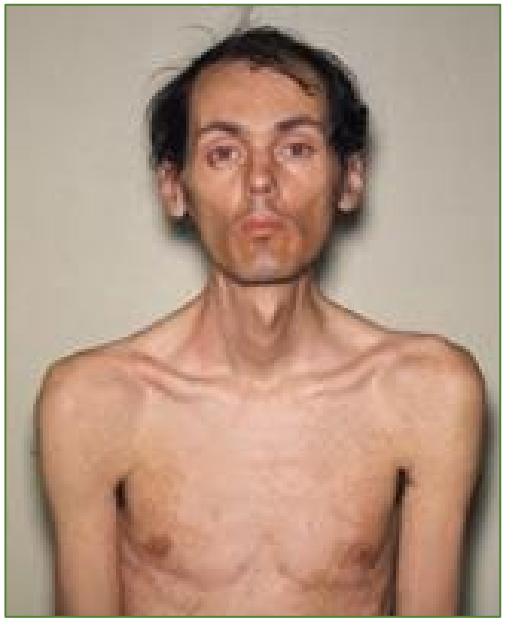
1. Norwood FL et al. Brain 2009;132:3175–3186.
2. Siciliano G et al. Clin Genet 2001;59:344–349
3. Johnson NE et al. Neurology 2021;96:e1045-e1053

Myotonic Dystrophy: Symptoms

- Cardinal symptoms of DM
  - Myotonia (inability for muscles to relax)
  - Progressive muscle weakness and wasting
- Non-muscular symptoms (% of patients)
  - EDS (~90%)
  - Fatigue (>90%)
  - Cognitive dysfunction (>60%)
- Other system involvement
  - Cardiac
  - GI
  - Endocrine





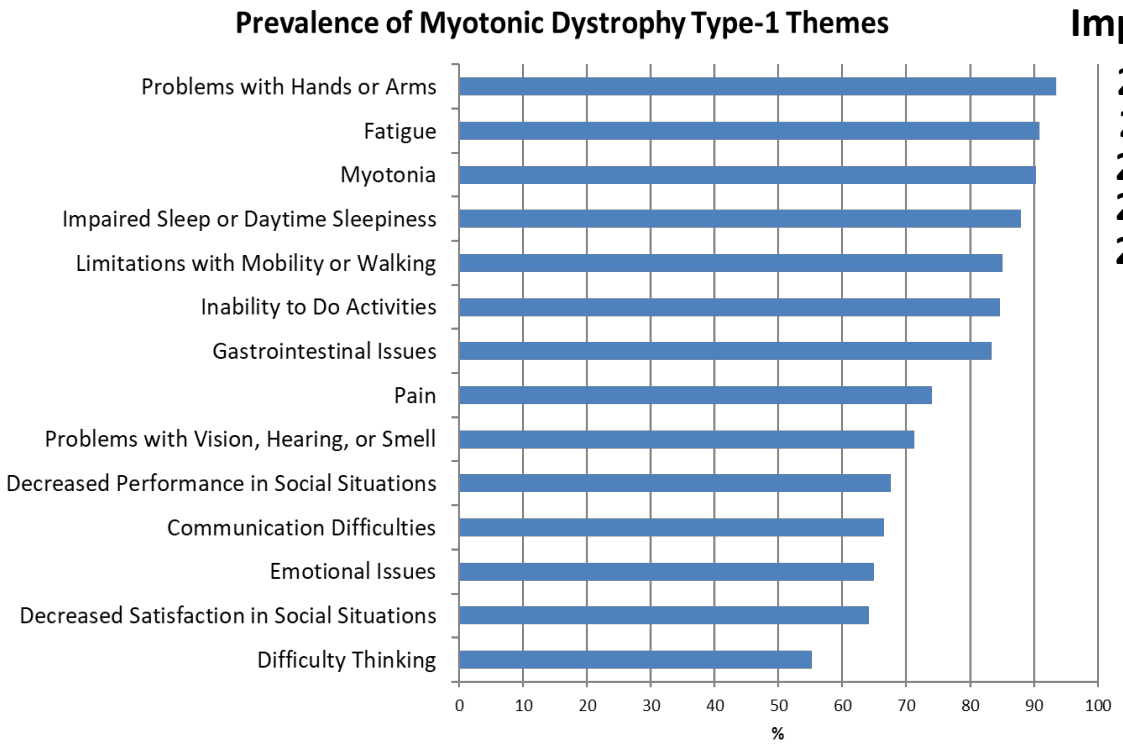


Source: Google image search for Myotonic Dystrophy

Prevalence and Impact of Symptoms in DM1: PRISM-1 Study

Key Findings:

- High prevalence of the non-muscular symptoms of EDS, fatigue and cognitive dysfunction
- Impact factor of EDS and fatigue as high (or higher) than muscular symptoms



Impact Factor (0 – 4)

2.27
2.49
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2.25
2.42

Patient-reported impact of symptoms in myotonic dystrophy type 1 (PRISM-1)

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Nicholas Johnson, MD
Christine Quinn, MS
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ABSTRACT

Objective: To determine the most critical symptoms in a national myotonic dystrophy type 1 (DM1) population and to identify the modifying factors that have the greatest effect on the severity of these symptoms.

Methods: We performed a cross-sectional study of 278 adult patients with DM1 from the national registry of patients with DM1 between April and August 2010. We assessed the prevalence and relative significance of 221 critical DM1 symptoms and 14 disease themes. These symptoms and themes were chosen for evaluation based on prior interviews with patients with DM1. Responses were categorized by age, CTG repeat length, gender, and duration of symptoms.

Results: Participants with DM1 provided symptom rating survey responses to address the relative frequency and importance of each DM1 symptom. The symptomatic themes with the highest prevalence in DM1 were problems with hands or arms (93.5%), fatigue (90.8%), myotonia (90.3%), and impaired sleep or daytime sleepiness (87.9%). Participants identified fatigue and limitations in mobility as the symptomatic themes that have the greatest effect on their lives. We found an association between age and the average prevalence of all themes ($p < 0.01$) and between CTG repeat length and the average effect of all symptomatic themes on participant lives ($p < 0.01$).

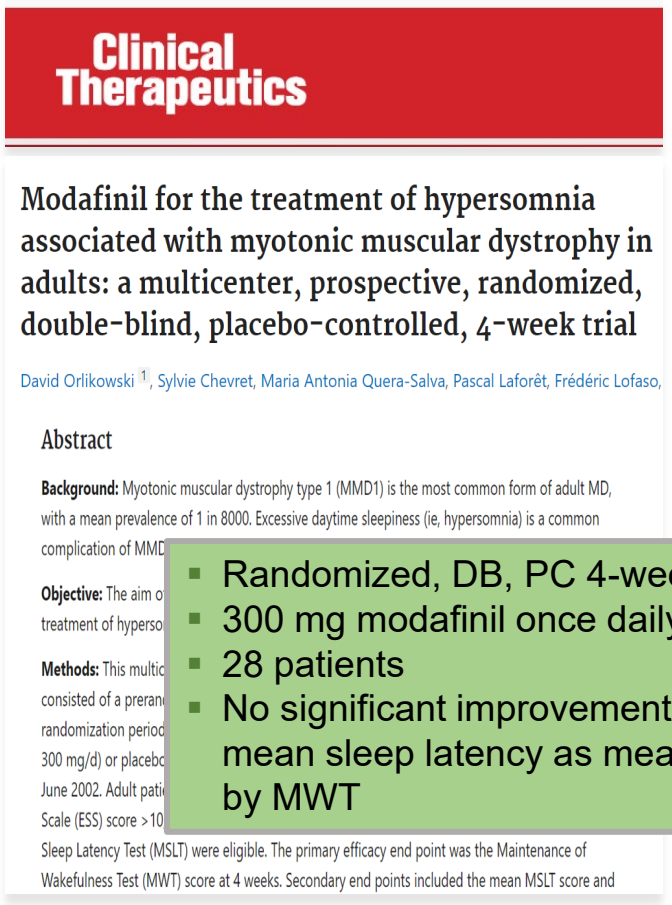
Conclusions: There are a wide range of symptoms that significantly affect the lives of patients with DM1. These symptoms, some previously underrecognized, have varying levels of importance in the DM1 population and are nonlinearly dependent on patient age and CTG repeat length. *Neurology*® 2012;79:1-1

GLOSSARY

DM1 = myotonic dystrophy type 1; **FDA** = Food and Drug Administration; **FSHD** = facioscapulohumeral muscular dystrophy; **PRISM-1** = Patient Reported Impact of Symptoms in Myotonic Dystrophy Type 1.

Heatwole C et al. Neurology 2012 Jul 24;79(4):348-57

Limited Current Treatment Options for Patients with DM



Clinical Therapeutics

Modafinil for the treatment of hypersomnia associated with myotonic muscular dystrophy in adults: a multicenter, prospective, randomized, double-blind, placebo-controlled, 4-week trial

David Orlikowski [1], Sylvie Chevret, Maria Antonia Quera-Salva, Pascal Laforêt, Frédéric Lofaso,

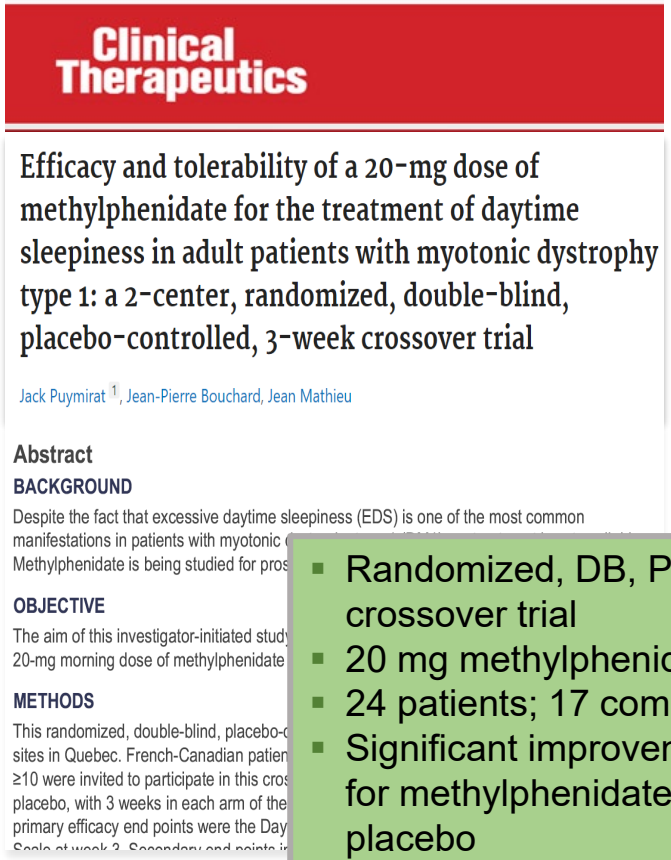
Abstract

Background: Myotonic muscular dystrophy type 1 (MMD1) is the most common form of adult MD, with a mean prevalence of 1 in 8000. Excessive daytime sleepiness (ie, hypersomnia) is a common complication of MMD

Objective: The aim o
treatment of hyperso

Methods: This multic
consisted of a prerar
randomization period
300 mg/d) or placebo
June 2002. Adult pati
Scale (ESS) score >10
Sleep Latency Test (MSLT) were eligible. The primary efficacy end point was the Maintenance of Wakefulness Test (MWT) score at 4 weeks. Secondary end points included the mean MSLT score and

- Randomized, DB, PC 4-week trial
- 300 mg modafinil once daily
- 28 patients
- No significant improvement on mean sleep latency as measured by MWT



Clinical Therapeutics

Efficacy and tolerability of a 20-mg dose of methylphenidate for the treatment of daytime sleepiness in adult patients with myotonic dystrophy type 1: a 2-center, randomized, double-blind, placebo-controlled, 3-week crossover trial

Jack Puymirat [1], Jean-Pierre Bouchard, Jean Mathieu

Abstract

BACKGROUND

Despite the fact that excessive daytime sleepiness (EDS) is one of the most common manifestations in patients with myotonic
Methylphenidate is being studied for pros

OBJECTIVE

The aim of this investigator-initiated study
20-mg morning dose of methylphenidate

METHODS

This randomized, double-blind, placebo-c
sites in Quebec. French-Canadian patien
≥10 were invited to participate in this cros
placebo, with 3 weeks in each arm of the
primary efficacy end points were the Day

- Randomized, DB, PC 3-week crossover trial
- 20 mg methylphenidate each morning
- 24 patients; 17 completers
- Significant improvement on the ESS for methylphenidate compared with placebo
  (-3.1 vs. -1.5; p = 0.039)
- No significant improvement on mean sleep latency as measured by MSLT

Significant unmet medical need for treatments for patients with DM

Common Patient Reflections

Key Themes of EDS, Fatigue & Cognition

2015 — The Christopher Project

- Completed by 450+ people with DM1 with **93%** reporting they experience EDS
- **Sleep** and **fatigue** issues can be pervasive and present a significant challenge on daily life
- Reported the use of 20 different **off-label medications** for EDS and/or fatigue with a mixed level of satisfaction

2016 — Patient-Focused Drug Development Meeting

- This meeting provided FDA the opportunity to hear directly from 58 DM patients, caregivers and advocates.
- **EDS**, **fatigue** and **cognitive function** highlighted as key non-muscular symptoms
- Three most important impacts for a new DM1 treatment: (1) **Reducing Fatigue**; (2) Improving Walking and Stamina; (2) **Improving Sleep Issues**

2017 — Annual Conference

- "*Bringing the Voice to CNS-Targeting Drug Development in Myotonic Dystrophy*" attended by 350 members of DM community
- Many patients reported CNS-related symptoms such as **EDS**, **fatigue** and **cognitive dysfunction** were a more significant burden than muscle weakness

2021 — Patient Advisory Board

- People and caregivers of people living with DM along with Harmony Clinical, Medical & Patient Advocacy
- Key Themes: **EDS**, **fatigue** and **cognition** are significant symptoms and there is a high interest in addressing this issue

https://www.myotonic.org/sites/default/files/pages/files/Christopher_Project_Full_Report.pdf

White, M. "Patient Input to Inform the Development of Central Nervous System Outcome Measures in Myotonic Dystrophy", Therapeutic Innovative and Regulatory Science, 2019

https://www.myotonic.org/sites/default/files/MDFVoicePatientReportMay2017.pdf

Common Patient Reflections
Key Themes of EDS, Fatigue & Cognition

the christopher project

"The experiences of patient respondents varies across the different 'types' of the disease, but DM1 respondents reported more daytime sleepiness and more impact from fatigue, and a harder time staying alert than Congenital DM and DM2 respondents."

Myotonic Dystrophy FOUNDATION

*"More than anything, I want to recapture the **joy of life** that can be lost to a neuromuscular disease that **requires most of my energy** to get through the day, leaving little reserve for the things that really matter."*

FDA

*"I hope, beg and pray for a drug or therapy that will help all the **brain-related symptoms** that DM1 patients are experiencing."*

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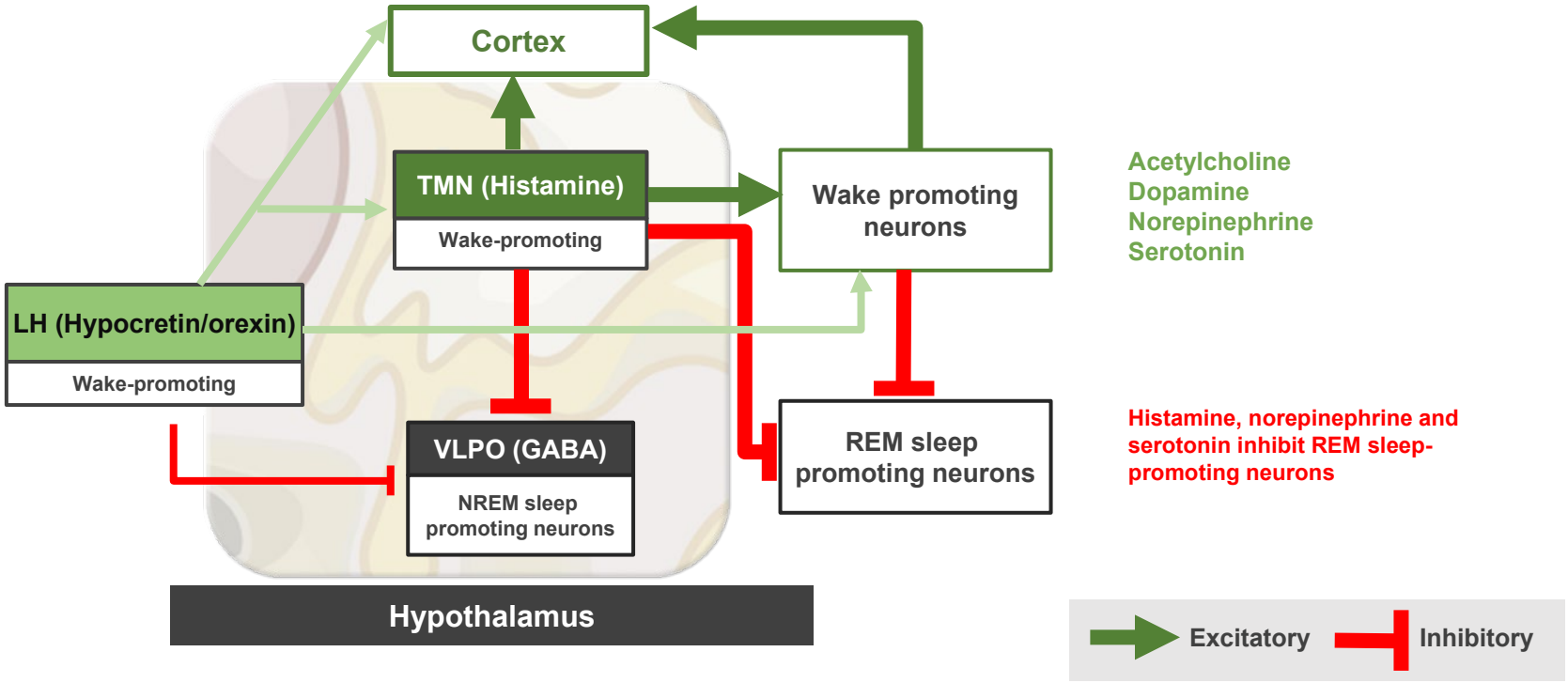
*"If I can go to a movie in a wheelchair that's ok for me as long as I'm able to **stay awake** during the whole movie."*

https://www.myotonic.org/sites/default/files/pages/files/Christopher_Project_Full_Report.pdf
White, M. "Patient Input to Inform the Development of Central Nervous System Outcome Measures in Myotonic Dystrophy", Therapeutic Innovative and Regulatory Science, 2019
https://www.myotonic.org/sites/default/files/MDFVoicePatientReportMay2017.pdf

Pitolisant: First-in-Class Molecule; Novel Mechanism of Action

- **Pitolisant -** Potent, highly selective histamine 3 (H_3) receptor antagonist/inverse agonist
  - Increases histaminergic transmission in the brain
  - Activates other wake promoting neurotransmitters (dopamine, norepinephrine, serotonin, acetylcholine)
    - Does not increase dopamine in the nucleus accumbens (consistent with its lack of abuse potential)

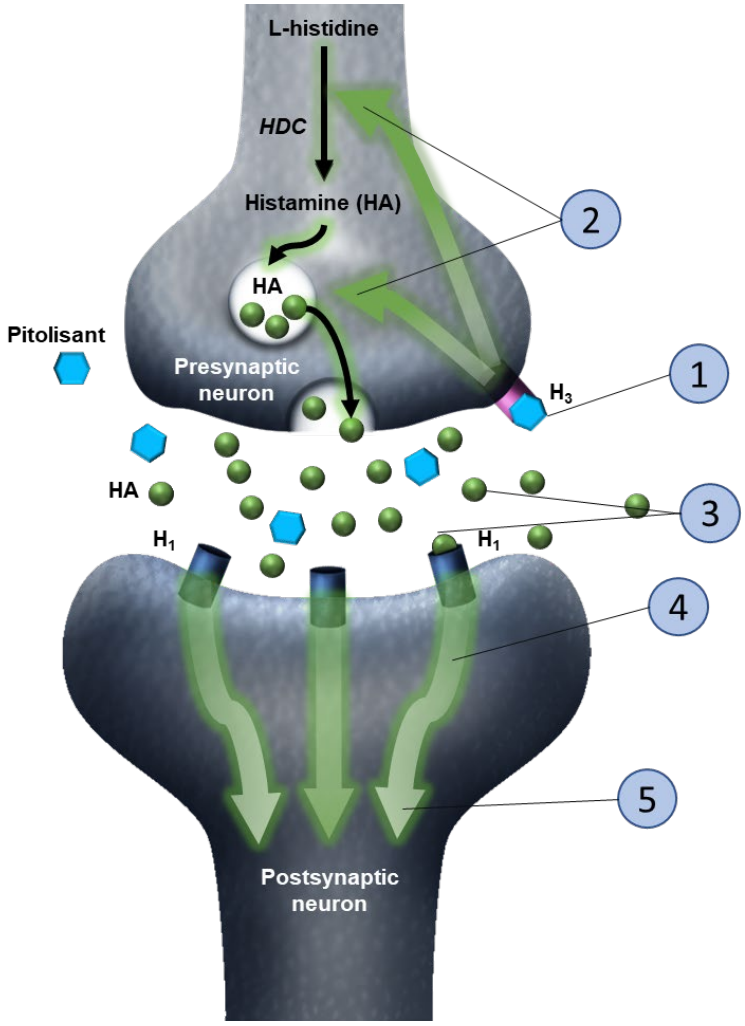
- Role of **histamine** in sleep-wake state stability (**3 H's**)



Pitolisant: Mechanism of Action

Pitolisant is a histamine H_3-receptor antagonist/inverse agonist that enhances the activity of histaminergic neurons in the brain[1-5]

1. Pitolisant binds to presynaptic H_3 autoreceptors, which blocks histamine binding to these receptors
2. Acting as an inverse agonist, pitolisant initiates increased histamine synthesis and release from vesicles into the synapse
3. This increased histamine in the synapse is then available to bind to excitatory postsynaptic H_1 receptors
4. Increased histamine binding at H_1 receptors results in an increase in neuronal firing of postsynaptic neurons
5. Increased firing of histamine neurons further activates wake-associated brain regions and further inhibits non-REM and REM sleep-associated brain regions



HA = histamine; HDC = L-histidine decarboxylase.

Figure adapted from: Benarroch EE. Neurology. 2010;75(16):1472-1479.

1. Lin JS, et al. *J Pharmacol Exp Ther.* 2011;336(1):17-23.
2. Schwartz JC. *Br J Pharmacol.* 2011;163(4):713-721.
3. Ligneau X, et al. *J Pharmacol Exper Ther.* 2007;320(1):365-375.
4. Lin JS, et al. *Neurobiol Dis.* 2008;30(1):74-83.
5. Uguen M, et al. *Br J Pharmacol.* 2013;169(3):632-644.

Pitolisant binds to H_3 receptors with a high affinity (K_i = 1 nM)

No appreciable binding to other histamine receptors (H_1, H_2, H_4; K_i ≥10 μM)

Rationale for Pitolisant in Patients with DM

EDS and fatigue most common non-muscular symptoms in patients with DM1

EDS experienced in up to 90% of patients and fatigue in > 90% of patients; both symptoms have high impact factor/BOI on par with muscular symptoms[1,2,3]

The hypothalamus regulates sleep-wake state stability via orexin and histamine

Decreased levels of orexin have been found in some patients with DM[4]

Role of histamine in disorders of orexin deficiency

Pitolisant increases histamine levels in the brain; demonstrated efficacy in improving daytime wakefulness

Histamine is one of the main neurotransmitters that mediates wakefulness, fatigue and cognition

Histamine also stimulates release of other key neurotransmitters in the brain (Ach, 5-HT,

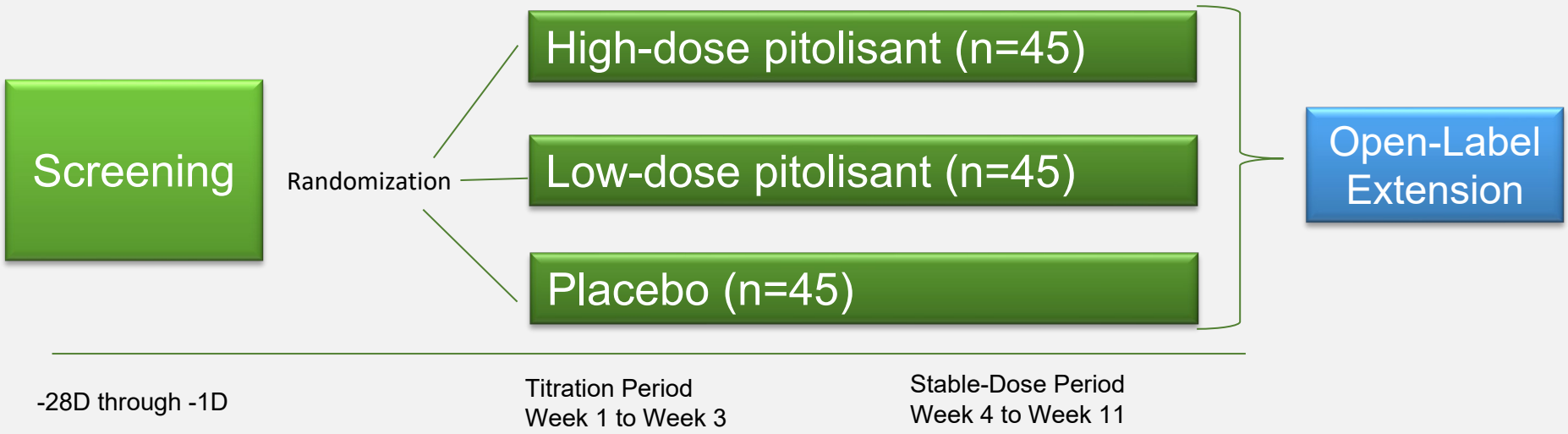
DA, NE)

Studies have suggested potential role of histamine and benefit of pitolisant in attention, vigilance, and cognitive function[5,6]

No FDA-approved treatments for patients with DM;
unmet medical need

1. Heatwole et al. *Muscle and Nerve*; 2016. 2. Dauvilliers et al, *Sleep Medicine Reviews*, 2012.
3. Hagerman et al, *Muscle Nerve*, 2019. 4. Martinez-Rodriguez et al. *Sleep*; 2003
5. Alvarez 2009. 6. Provensi et al. 2018.

Phase 2 Clinical Trial of Pitolisant in Patients with DM1



Trial Design:

- Randomized, double-blind, placebo-controlled, parallel-group study
- ~135 patients; ages 18 – 65
- ~20 clinical trial sites

Objectives:

- Primary objective: to evaluate the safety and efficacy of pitolisant compared with placebo in treating EDS in patients with DM1
- Secondary objectives: to assess the impact of pitolisant on fatigue, cognitive function, patient assessment of overall disease burden, clinician assessment of overall disease severity, and long-term safety and effectiveness in patients with DM1

Concluding Remarks

- Mechanism-based approach to LCM development programs for pitolisant based on its unique MOA
  - Decreased orexin levels seen in both DM and PWS

- Strong scientific rationale for potential utility of pitolisant in patients with DM
  - EDS, fatigue and cognitive function mediated through histaminergic circuits in the CNS along with other neurotransmitters that are stimulated by histamine and H_3 receptors

- DM1 represents potential large market opportunity for pitolisant
  - Affects ~160,000 people in US
  - EDS, fatigue and cognitive dysfunction most common non-muscular symptoms
  - No FDA-approved treatments → significant unmet medical need

- On track to initiate Phase 2 trial by the end of the month

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