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Advances in NMDs Therapies.

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Disclosures

- Consulting Fee (e.g., Advisory Board)
  - UCB Pharma Company, Alexion Pharmaceuticals
- Speakers' Bureau
  - UCB Pharma Company

Objectives;

- Highlight advances lead to recent novel therapies.
- List NMDs with recent advances in therapies.
- Briefly create awareness of new therapies.

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Driving Novel Therapies

- Novel treatments of rare NMD is evolving for the last 5-7 years.
- Advances in pharmacology & cell biology leading more targeted treatments.
- Advances in genetics and diagnostic studies have enabled better understanding and enabled new therapies.
- Orphan Drug Act of 1983 accelerated development of novel treatments for rare NMD.
- The goal is alerting to what agents are approved or in the pipeline

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Information

Diseases with approved new therapies

- Myasthenia Gravis
- Duchenne Muscular Dystrophy
- Spinal Muscular Atrophy (SMA)
- Periodic Paralysis
- Lambert-Eaton myasthenic syndrome (LEMS)
- Mitochondrial myopathy
- Polyneuropathy of hereditary transthyretin-mediated amyloidosis.

Diseases with research therapies in the pipeline

- Hereditary motor sensory neuropathy (CMT).
- Inclusion body myositis (IBM)
- Sporadic ALS

Fascioscapulohumeral muscular dystrophy (FSH)

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GENERALIZEDMYASTHENIA GRAVIS

- Several drugs for generalized myasthenia gravis such as inhibitors of the neonatal Fc receptor and complement C5, Including **rozanolixizumab** and **zilucoplan** provide a quicker clinical response .

- Other drug targets are also being explored in MG, including inhibition of IL-6, modified B-cell depletion, and immune-tolerising approaches.

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- **Duchnne Muscular Dystrophy;**
  - **Eteplirsen** an exon-skipping therapy 2016.
  - **Deflazacort** a corticosteroids option 2017.
  - **Golodirsen** 53 exon skipping mutation 2019.
  - **Viltolarsen** 53 exon skipping mutation 2020.
  - **Delandisttrogene** mutation in the DMD gene 2023

- **Spinal Muscular Atrophy (SMA)**

Therapeutic strategies thru enhancing SMN protein by either;

I - by Antisense oligonucleotide (ASO) **Nusinersen**

- or by Splicing modifier of SMN2 protein **Risdiplam**

II- or replacing the function of faulty SMN1 gene thru Vector delivered replacement DNA **Onasemnogene**

- **Lambert Eaton Syndrome (LES)**

- **Amifampridine** potassium channels blocker 2018.

- **Mitochondrial Myopathy;**

- Various vitamins, cofactors, and small molecules have failed to show definitive benefit
- New molecular strategies, specifically through use of a designer nuclease platform optimized for delivery to mitochondria targeted zinc finger-nuclease (mtZFNs) offer hope for the future. (PMD 30155814)

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Transthyretin-Related Amyloidosis (TTR) approved treatment;

- **Patisiran** small molecule causes degradation of TTR mRNA, 2018
- **Inotersen** an ASO weekly SC injections 15 months lower TTR 75% and 20-point benefit vs 7 point placebo 2018
- Liver transplant helpful in certain but not all mutations
- **Tafamidis & Diflunisal** in ATTRv stabilizes TTR tetramer delayed progression of neurological impairment 2013

Hereditary ALS

- **tofersen** is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 *(SOD1)* gene based on reduction in plasma neurofilament light chain (NfL) 100 mg intrathecally , April 2023.

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Raised Comments and Questions

Insurance Covered Treatment;

- Based on published trial inclusion/exclusion criteria
- Not for patients outside age or severity of clinical trial.
- Reauthorization only if treatment continues to work

Obstacle;

- Does slowed rate of decline signify treatment efficacy?
- How to show slowed rate of decline in an individual patient?
- What level of disease severity is worth stabilizing?

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