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# ORPHAN DISEASE TREATMENT

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**ABSTRACT**

- *Background and aims: Orphan diseases, or rare diseases, are defined in Europe as diseases that affect less than 5 out of every 10,000 citizens. Given the small number of cases and the lack of profit potential, pharmaceutical companies have not invested much in the development of possible treatments.*
- *However, over the last few years, new therapies for rare diseases have emerged, giving physicians a chance to offer personalized treatment. With this paper, we aim to present some of the orphan neurological diseases for which new drugs have been developed lately.*
- *MethodsWe have conducted a literature review of the papers concerning rare diseases and their treatment, and we have analyzed the existing studies for each orphan drug. For this purpose, we have used the Google Scholar search engine and the Orphanet.*
- *We have selected the studies published in the last 15 years. Results. Since the formation of the National Organization for Rare Diseases, the Orphan Drug Act, and the National Institutes of Health Office of Rare Diseases, pharmacological companies have made a lot of progress concerning the development of new drugs.*
- *Therefore, diseases that until recently were without therapeutic solutions benefit today from personalized treatment*
- *We have detailed in our study over 15 neurological and systemic diseases with neurological implications, for which the last 10–15 years have brought important innovations regarding their treatment.Many steps have been taken towards the treatment of these patients, and the humanity and professionalism of the pharmaceutical companies, along with the constant support of the patient's associations for rare diseases, have led to the discovery of new treatments and useful future findings*

## INTRODUCTION

Orphan diseases, also known as rare diseases, affect a small percentage of the population, often leaving patients with limited treatment options. This project aims to review existing medications and potential therapeutic approaches for rare diseases, highlighting the challenges and opportunities in orphan disease treatment.

Orphan diseases, affecting approximately 3.5% of the global population, have long been neglected due to limited market incentives and lack of awareness. However, recent years have witnessed significant progress in orphan disease treatment, driven by advances in genetics, precision medicine, and collaborative research efforts.

Orphan diseases are rare diseases, defined in Europe as having an incidence lower than 5 per 10,000 citizens. It is not unusual for a family doctor to encounter less than one such case per year. Because of this, there is also a delay in the diagnosis process and the decision-making process, with studies showing that approximately half of the patients with rare diseases receive on average one misdiagnosis.

Some of the pathologies may be congenital and present from birth, while others appear during adulthood. There are rare new diseases being described every week in the medical literature, with a total of over 6000 orphan diseases. Because of the lack of profit potential and the costs and logistics necessary to organize clinical trials for these pathologies, the development of specific therapies is not a priority for pharmaceutical companies

Beginning in 1982, signs of progress were made concerning the research in this field, with the foundation of the National Organization for Rare Diseases (NORD) and the approval of the Orphan Drug Act by the Congress of the United States.

These encouraged the pharmaceutical companies by providing tax relief to those who participated in the research for new orphan drugs. It would also assure a 7- year exclusivity for the product if used for the treatment of an orphan disease .Orphan diseases, also known as rare diseases, affect millions of people worldwide, yet they remain largely neglected in terms of research, diagnosis, and

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## CLASSIFICATION OF ORPHAN DISEASE

**A) On the genetic basis**

1. **Genetic Orphan Diseases:** These are caused by mutations or alterations in a person's DNA.
   Examples include:
   - Cystic Fibrosis: A genetic disorder that affects the lungs and digestive system.
   - Duchenne Muscular Dystrophy (DMD): A severe form of muscular dystrophy caused by a mutation in the dystrophin gene.
2. **Non-Genetic Orphan Diseases:** These are not primarily caused by genetic factors. They might result from infections, environmental factors, or unknown causes.
   Examples include:
   - Idiopathic Pulmonary Fibrosis: A chronic lung disease with no known specific cause.
   - Primary Biliary Cholangitis: An autoimmune disease that affects the bile ducts in the liver.

**B) By Body System Affected**

1. Neurological Orphan Diseases: Affect the nervous system.
   - Amyotrophic Lateral Sclerosis (ALS): A progressive neurodegenerative disease affecting motor neurons.
2. Hematological Orphan Diseases: Affect the blood or bone marrow.
   - Paroxysmal Nocturnal Hemoglobinuria (PNH): A rare, life-threatening disease of the blood.
3. Metabolic Orphan Diseases: Involve metabolic pathways.
   - Phenylketonuria (PKU): A metabolic disorder caused by a deficiency of the enzyme phenylalanine hydroxylase**.**
4. Cardiovascular Orphan Diseases: Affect the heart or blood vessels.
   - Pulmonary Arterial Hypertension (PAH): A type of high blood pressure that affects arteries in the lungs and the heart.

**C). By Prevalence and Geographic Distribution**

1. Ultra-Rare Diseases: Affect fewer than one in a million people.
   a. Fibrodysplasia Ossificans Progressiva (FOP): A disorder where soft tissues progressively turn into bone.
2. Rare Diseases with Regional Prevalence: These may be more common in specific regions due to genetic, environmental, or cultural factors. Sickle Cell Disease: More prevalent in Sub-Saharan Africa, India, and the Middle East due to genetic inheritance patterns.
3. Globally Rare Diseases: Diseases that are rare worldwide.
   a. Gaucher Disease: A genetic disorder where fatty substances accumulate in cells and certain organs.

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**D). By Prevalence and Geographic Distribution**

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## CYSTIC FIBROSIS (CF)

**Treatment**

CFTR Modulators:

- Ivacaftor: Helps improve the function of the CFTR protein in specific mutations, allowing better chloride ion transport.
- Lumacaftor: Works to stabilize the defective CFTR protein, improving its function.
- Combination Therapies: Ivacaftor and lumacaftor are often used together to address different aspects of CFTR dysfunction in various mutations.

Chest Physiotherapy:

- Techniques like postural drainage, vibratory devices, and high-frequency chest wall oscillation (HFCWO) are used to help clear thick mucus from the lungs.
- Regular sessions (multiple times per day) are crucial for preventing infections and maintaining lung function.

Enzyme Replacement Therapy:

- Pancreatic enzymes (such as lipase, amylase, and protease) are taken with meals to aid digestion, as CF blocks enzyme release from the pancreas.
- Helps improve nutrient absorption and prevents malnutrition.

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## CHARACTERISTIC OF ORPHAN DISEASE

**A) Epidemiological Characteristics**

1. Rarity: Affects fewer than 200,000 people in the US or 5 in 10,000 people in the EU.
2. Low prevalence: Less than 5% of the population.
3. High mortality rate: Many orphan diseases are life-threatening.

**B) Clinical Characteristics**

1. Serious or life-threatening: Significant impact on quality of life.
2. Chronic or progressive: Long-term or worsening condition.
3. Debilitating symptoms: Pain, disability, or cognitive impairment.
4. Limited treatment options: Few or no effective treatments.

**C) Genetic Characteristics**

1. Genetic basis: Many orphan diseases have a genetic origin.
2. Mutations: Changes in DNA sequence or gene expression.

**D) Pathophysiological Characteristics**

1. Complex biology: Involves multiple biological pathways.
2. Multisystem involvement: Affects multiple organs or systems.
3. Heterogeneous presentation: Variable symptoms and severity.

## ORGANIZATION WORKING ON ORPHAN DISEASE TREATMENT

1. National Organization for Rare Disorders (NORD)

* Location: United States

* Overview: NORD is a leading advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. NORD provides patient assistance programs, promotes research, and advocates for public policies that support the rare disease community.

2. European Organisation for Rare Diseases (EURORDIS)

* Location: Europe

* Overview: EURORDIS is a non-governmental alliance of patient organizations and individuals active in the field of rare diseases. It works to build a strong panEuropean community of patient organizations and people living with rare diseases.

3. Genetic and Rare Diseases Information Center (GARD)

* Location: United States

* Overview: GARD, operated by the National Institutes of Health (NIH),provides comprehensive information about genetic and rare diseases to patients, their families, healthcare providers, and researchers.

4. The International Rare Diseases Research Consortium (IRDiRC)

* Location: International

* Overview: IRDiRC is a global initiative that unites research funding organizations, patient advocacy groups, and industry partners to foster and coordinate research on rare diseases. The goal is to accelerate the development of diagnostics and therapies for rare diseases

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**Challenges Faced by Orphan Disease Patients**

- Diagnosis Delay: Due to their rarity, orphan diseases are often misdiagnosed or not recognized by healthcare providers, leading to delayed or incorrect treatment.
- Lack of Treatments: Pharmaceutical companies are often unwilling to invest in developing treatments for rare diseases due to the small number of patients. As a result, many orphan diseases have no approved treatments or only limited options.
- High Cost of Care: For many rare diseases, treatment options that do exist can be prohibitively expensive. Moreover, patients may need to see multiple specialists, further adding to the financial burden.
- Limited Research: Orphan diseases often receive insufficient research funding, and the scientific community may not have the knowledge or infrastructure needed to conduct studies. As a result, there is limited understanding of the underlying causes and potential treatments for these diseases.

## LITERATURE SURVEY

1. Bell and Tudur Smith (2014)et.al: provide a comprehensive review of the classification systems used for orphan diseases, discussing the challenges in developing standardized treatments. Their work emphasizes the role of personalized medicine in addressing the heterogeneous nature of orphan diseases, which often require individualized therapeutic approaches (Bell & Tudur Smith, 2014).
2. Melnikova (2012)et.al: focuses on the innovations in rare disease research and orphan drug development. The article discusses how new technologies, such as next-generation sequencing, are facilitating the discovery of rare disease genes and the development of targeted therapies (Melnikova, 2012).
3. Mullard (2019)et.al: provides an overview of FDA drug approvals, highlighting the increasing number of orphan drugs being approved. This trend underscores the growing recognition of the need for effective therapies for rare diseases (Mullard, 2019).
4. Kay (2011)et.al: reviews the state-of-the-art gene-based therapies for orphan diseases, discussing the progress made in gene therapy and the road ahead. The author highlights the potential of gene therapy to provide long-term or curative treatments for many rare diseases (Kay, 2011).
5. Drummond et al. (2007)et.al analyzed the economic challenges posed by orphan drugs. The high costs of research and development (R&D), coupled with the small patient populations, make these therapies financially challenging. The authors call for alternative pricing models and public health policies to ensure patient access to these essential treatments (Drummond et al., 2007)
6. Austin, Dawkins, and Collier (2017)et.al: describe the role of the International Rare Diseases Research Consortium (IRDiRC) in uniting researchers and fostering global collaboration. Their work emphasizes the importance of collaborative efforts in advancing rare disease research and treatment (Austin et al., 2017).
7. Maria Luísa Bouwman et al.(2018) Orphan medicines are medicinal products intended for the diagnosis, prevention, or treatment of life-threatening or debilitating rare diseases.

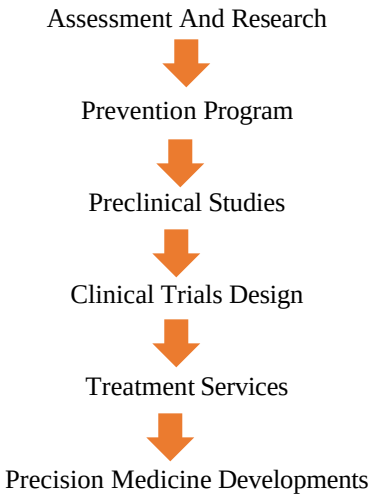
**AIM:** Orphan disease treatment: focus on medication for rare diseases that have limited treatment options

**OBJECTIVES**

1. To identify areas for future research and development in rare disease treatment: This objective aims to highlight the gaps in current knowledge and understanding, and to suggest areas for future research and development.
2. To discuss the potential of rare disease treatment in improving public health outcomes: This objective seeks to explore the broader implications of rare disease treatment for public health outcomes and healthcare systems.
3. To examine the role of patient advocacy and engagement in rare disease treatment: This objective aims to investigate the importance of patient advocacy and engagement in shaping rare disease treatment and research agendas.
4. To provide a comprehensive overview of current treatments for orphan diseases.
5. To identify the challenges and limitations of current treatments for orphan diseases.
6. To discuss emerging therapies and innovative approaches for orphan disease treatment.
7. To examine the role of personalized medicine in orphan disease treatment.
8. To analyze the impact of orphan disease treatment on patient outcomes and quality of life.
9. To review the regulatory frameworks and policies governing orphan disease treatment.
10. To identify areas for future research and development in orphan disease treatment.
11. To discuss the potential of orphan disease treatment in improving public health outcomes

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## PLANE OF WORK




## CURRENT TREATMENTS

### 1. Approved Orphan Drugs

- Targeted Therapies: Some orphan diseases have specific drugs that have been developed and approved through regulatory pathways like the FDA's Orphan Drug Designation. These drugs are designed to target the underlying mechanisms of the disease.
  Examples: Ivacaftor (Kalydeco): Used for certain mutations in cystic fibrosis.
  Eculizumab (Soliris): Used for treating Paroxysmal Nocturnal Hemoglobinuria (PNH) and atypical Hemolytic Uremic Syndrome (aHUS).
- Enzyme Replacement Therapy (ERT): For diseases caused by enzyme deficiencies, such as certain lysosomal storage disorders, ERT provides the missing enzyme.
  Examples: Imiglucerase (Cerezyme): Used for Gaucher disease. Laronidase (Aldurazyme): Used for Mucopolysaccharidosis type I (MPS I).

### 2. Off-Label Use of Existing Medications

Repurposing Drugs: Since many orphan diseases lack approved treatments, physicians often prescribe drugs that are approved for other conditions but have shown some efficacy in treating the symptoms or slowing the progression of a rare disease.
Examples: Sirolimus: Originally an immunosuppressant for organ transplants, used offlabel for Lymphangioleiomyomatosis (LAM).
Hydroxyurea: Used off-label in managing sickle cell disease.

Gene Therapy

- Emerging Field: Gene therapy has become one of the most promising treatment options for certain orphan diseases, particularly those with a clear genetic cause. This approach aims to correct or replace the faulty genes responsible for the disease.
  Gene therapy is an experimental technique to treat and prevent diseases by altering human genes Adenoviral vector is one of the most commonly used viral vectors in gene therapy. It is capable of treating not only hematological diseases such as hemophilia, gaucher disease, and hemochromatosis, but also has made significant progress in treating genetic diseases, rare diseases, and tumors Inheritance is a critical factor in rare diseases.
  Examples: Luxturna (voretigene neparvovec): Used to treat inherited retinal diseases caused by mutations in the RPE65 gene.
  Zolgensma (onasemnogene abeparvovec): Used for spinal muscular atrophy (SMA), delivering a functional copy of the SMN1 gene.

### 3. Stem Cell and Bone Marrow Transplantation

- Curative Potential: For certain genetic and hematologic orphan diseases, stem cell or bone marrow transplantation can offer a potential cure by replacing the defective cells with healthy ones. Hematopoietic stem cell transplantation (HSCT) is a treatment modality that uses human cells to modulate the immune system or to provide educational support. There are several pathways of transplantation for HSCT, including fetal liver cell transplantation, bone marrow transplantation, peripheral hematopoietic stem cell transplantation, and umbilical cord blood transplantation. Many clinical practices and applications have demonstrated that cord blood has beneficial effects in treating rare diseases.

Examples:
Hematopoietic Stem Cell Transplantation: Used in severe cases of sickle cell disease, thalassemia, and certain immunodeficiencies.

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Bone Marrow Transplant: A treatment option for severe combined immunodeficiency (SCID) and some types of leukodystrophies.

## FUTURE DIRECTION

### Personalized Medicine

1. Development of targeted therapies: Researchers will focus on creating targeted therapies tailored to individual patients' genetic profiles. This approach will help optimize treatment outcomes and minimize side effects.
2. Increased use of biomarkers: Biomarkers will play a crucial role in predicting treatment response and monitoring disease progression. This will enable healthcare providers to make informed decisions about treatment strategies.

### Gene Therapy

1. Advancements in gene editing technologies: Gene editing technologies like CRISPR/Cas9 will continue to advance, enabling more precise and efficient gene editing.
2. Development of gene therapies: Gene therapies will be developed for rare genetic disorders, offering new hope for patients with previously untreatable conditions.

### Stem Cell Therapy

1. Research into regenerative medicine: Researchers will explore the potential of stem cells for regenerative medicine, focusing on their ability to repair or replace damaged tissues.
2. Development of stem cell therapies: Stem cell therapies will be developed for rare diseases, such as muscular dystrophy, offering new treatment options for patients.

### RNA Therapies

1. Development of RNA-based therapies: Researchers will focus on developing RNA-based therapies, including RNA interference (RNAi) and antisense oligonucleotides.
2. Research into RNA therapies for rare diseases: RNA therapies will be investigated for their potential to treat rare diseases, such as spinal muscular atrophy.

## CONCLUSION

Orphan diseases, despite their rarity, represent a significant and growing challenge in global healthcare. The complexity and diversity of these conditions, coupled with the small patient populations, have historically resulted in limited treatment options and a lack of awareness. However, advancements in biotechnology, genomics, and personalized medicine are beginning to change this landscape.

Innovative approaches, including gene therapy, drug repurposing, and the use of advanced diagnostic tools, hold great promise for the future. Collaborative efforts among researchers, patient advocacy groups, and industry stakeholders are essential to drive progress and overcome the unique obstacles associated with orphan diseases. Additionally, ongoing support for patient-centered research, coupled with a global commitment to improving rare disease infrastructure, will be crucial in ensuring that all patients have access to the care they need.

This review aims to provide an overview of the current state of orphan disease treatment, highlighting recent advances, challenges, and future directions. We will discuss the various approaches being explored, including gene therapy, stem cell therapy, RNA therapy, and precision medicine, and examine the potential of these approaches to transform the lives of patients with orphan diseases.

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