Exploring the landscape of orphan and rare diseases


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1. Introduction

Global health care is getting closer to reality by the efforts of numerous national government and non-governmental organisations, as well as international organisations like the World Health Organisation (WHO) and the United Nations Children's Fund. The major global health challenges were to develop the strategies for treating orphan and rare disease.

The terms "orphan diseases" and "rare diseases" are often used interchangeably, but they have slightly different connotations. “Rare diseases" refer to those medical conditions which affect a small percentage of the population. In the United States, a disease is considered rare if it affects fewer than 200,000 people (1). However, definitions of rare diseases may vary by country, while orphan diseases specifically refer to rare diseases that have been neglected by the medical and pharmaceutical industries. The term "orphan" originally came from the lack of attention these diseases received, akin to orphaned children who lacked support and care. The development of treatments for orphan diseases was historically limited due to the small number of patients affected, making them unprofitable for pharmaceutical companies and moreover the pharmaceutical companies also showed little interest in developing treatments for these conditions because they were not financially viable. However, in recent years, there has been growing awareness and efforts to address the needs of patients with rare diseases. Governments, advocacy groups, and research organizations have been working to promote research, increase funding, and develop policies to support the development of therapies for orphan diseases.

The concept of orphan diseases, or rare diseases, gained attention in the 1970s when patients and advocacy groups began to raise awareness about the lack of research, funding, and treatments for these conditions. The term "orphan disease" was coined to reflect the neglected status of these disorders, likening them to orphaned children who lacked support and attention (2,3).

The laws pertaining to orphan drugs differ among industrialised nations and were initially implemented in the US in 1983, Singapore in 1991, Japan in 1993, Australia in 1997, and the EU in 2000 (4). Rare diseases, also referred to as orphan diseases are medical conditions that affect a small percentage of the population. The rare disease according to US definition is one that affects less than 200,000 individuals, the corresponding number in Australia is 2000 and in Japan is 50000 (5). While each rare disease individually affects a small number of people, collectively they impact millions worldwide. These diseases often pose significant challenges for patients and their families due to the lack of effective treatments, limited understanding, and difficulty in diagnosis.

The Orphan Drug Act of 1983 in the United States was a landmark piece of legislation aimed at incentivizing pharmaceutical companies to develop treatments for rare diseases. Before this act, there was little economic incentive for drug companies to invest in researching and developing therapies for diseases that affected only a small number of individuals. The Orphan Drug Act provided financial incentives, such as tax credits and marketing exclusivity, to encourage companies to pursue orphan drug development. The Orphan Drug Act was a turning point in the history of orphan diseases, leading to increased research and development efforts for rare conditions. It helped to bring attention to the unique challenges faced by patients with rare diseases and paved the way for the development of treatments for many previously neglected disorders.

Since the advent of the Orphan Drug Act, there has been significant progress in the field of rare diseases. Advances in genetics, molecular biology, and medical technology have improved our understanding of many rare conditions, leading to earlier diagnosis and the development of targeted therapies. Furthermore, patient advocacy groups have played a vital role in raising awareness, supporting research, and providing resources for individuals and families affected by rare diseases.

Despite these efforts, many challenges remain including diagnosis, which can be a long and frustrating process, often involving visits to multiple specialists and numerous tests. Additionally, once diagnosed, patients may struggle to access appropriate medical care and treatments due to limited availability or high costs.

Furthermore, because these diseases are often poorly understood, there may be a lack of information and resources for patients and their families. Support groups and some organizations play a crucial role in giving support, providing education and resources to individuals affected by rare diseases. Overall, while progress has been made in addressing the needs of patients with rare diseases, much more work is needed to improve diagnosis, treatment, and support for those living with these conditions.

The Orphan Drug Act of 1983 in the United States was instrumental in incentivizing the development of treatments for orphan diseases by providing financial incentives to pharmaceutical companies. There are thousands of rare diseases affecting individuals worldwide. Each rare disease presents its own set of challenges in terms of diagnosis, treatment, and management, often requiring specialized care and support from healthcare professionals and advocacy groups.Some rare diseases and the specific disorders are listed in Table 1.

Table 1. List of some rare diseases and their specific disorders

RARE DISEASES RELATED TO GENETIC DISORDERS	
Huntington's Disease	Muscle coordination is affected in this genetic neurodegenerative disorder which leads to cognitive decline and psychiatric problems. It's caused by a mutation in the HTT gene.
Cystic Fibrosis	A genetic disorder that affects the lungs and digestive system, causing difficulty in breathing and poor growth. It's caused by mutations in the CFTR gene
Pompe Disease	Caused by mutations in the GAA gene, leading to a deficiency of the enzyme acid alpha-glucosidase (GAA) in this genetic disorder. It results in the buildup of glycogen in tissues, particularly in muscles, leading to muscle weakness and other symptoms
Gaucher Disease	A genetic disorder caused by mutations in the GBA gene, leading to a deficiency of the enzyme glucocerebrosidase. It results in the accumulation of certain lipids in cells, particularly in the spleen, liver, and bone marrow, leading to symptoms such as enlargement of these organs, anaemia, and bone problems.
Progeria (Hutchinson-Gilford Progeria Syndrome)	This rare genetic condition causes rapid aging in children, leading to features such as premature aging of the skin, hair loss, joint abnormalities, and cardiovascular problems.
Fibrodysplasia Ossificans Progressiva (FOP)	FOP is an exceedingly rare hereditary condition characterised by the progressive formation of bone outside the skeleton (heterotopic ossification) from muscle and connective tissue. This procedure impairs mobility and may result in serious impairment.
Niemann-Pick Disease	It is a group of rare genetic disorders characterized by the abnormal accumulation of lipids (fats) in cells throughout the body. Symptoms vary depending on the type of Niemann-Pick disease but may include hepatosplenomegaly (enlargement of the liver and spleen), neurological problems, and respiratory difficulties.
RARE DISEASES RELATED TO METABOLIC DISORDERS	
Alkaptonuria	A rare metabolic disorder caused by a deficiency of the enzyme homogentisate-1,2-dioxygenase, which leads to the accumulation of homogentisic acid, which can cause darkening of the urine, joint problems, and other health issues.
Gaucher Disease	It is caused by a deficiency of an enzyme called glucocerebrosidase. This enzyme deficiency leads to the accumulation of a type of fat molecule called glucocerebroside within cells, particularly in the spleen, liver, and bone marrow.
Niemann-Pick Disease	It is caused by the deficiency of an enzyme called acid sphingomyelinase (ASM), leading to the accumulation of sphingomyelin within cells, particularly in the liver, spleen, and brain.

Fabry disease	Characterized by the deficiency of an enzyme called alpha-galactosidase A, leading to the buildup of fatty substances in various organs, causing symptoms such as pain, skin lesions, kidney problems, and cardiovascular complications.
Wilson disease	Characterized by the deficiency of an enzyme called alpha-galactosidase A, leading to the buildup of fatty substances in various organs, causing symptoms such as pain, skin lesions, kidney problems, and cardiovascular complications.
RARE DISEASE RELATED TO AUTOIMMUNE DISORDERS	
Wegener's Granulomatosis	It is a rare autoimmune disorder characterized by inflammation of blood vessels, leading to damage in various organs such as the lungs, kidneys, and upper respiratory tract.
Systemic Lupus Erythematosus (SLE)	A chronic autoimmune disease affecting multiple organs, causing inflammation and tissue damage throughout the body.
Scleroderma	Characterized by excessive collagen production, leading to thickening, and hardening of the skin and connective tissues, a rare autoimmune disorder.
Behçet's Disease	It is a rare autoimmune disorder characterized by recurrent inflammation of blood vessels, resulting in oral and genital ulcers, skin lesions, and eye inflammation.
Kawasaki Disease	This rare autoimmune disorder primarily affects children and causes inflammation of blood vessels throughout the body, leading to symptoms like rash, high fever, redness, swollen lymph nodes, and swelling of the hands and feet.
RARE DISEASES RELATED TO NEUROLOGICAL DISORDERS	
Amyotropic Lateral Sclerosis (ALS)	Also known as Lou Gehrig's disease, is a progressive neurodegenerative disease which affects nerve cells of the brain and spinal cord, leading to muscle weakness with paralysis.
Narcolepsy	A neurological disorder characterized by excessive daytime sleepiness and sleep attacks, with sudden loss of muscle tone (cataplexy). It's thought to be caused by a combination of genetic and environmental factors
Guillain-Barré Syndrome (GBS)	It is a rare neurological disorder where peripheral nerves are attack by the body's immune system causing muscle weakness, numbness, and, in severe cases, paralysis. It often follows a viral or bacterial infection and can lead to life-threatening complications if not treated promptly.
Spinocerebellar Ataxia (SCA)	It refers to a group of inherited neurological disorders characterized by progressive degeneration of the cerebellum and spinal cord, leading to problems with coordination and balance. Symptoms typically include gait ataxia, dysarthria, and may involve other neurological impairments such as tremors and muscle stiffness.

RARE CANCER DISEASES	
Mesothelioma	It is a rare disorder that initially affects the lining of the lungs but may also occur in the lining of the abdomen or heart. It is mostly caused by exposure to asbestos and is associated with symptoms like chest pain, shortness of breath, and weight loss.
Pancreatic Neuroendocrine Tumors (PNETs)	These are rare tumours that develop from neuroendocrine cells in the pancreas and can be non-functional or produce hormones. Symptoms vary widely but may include abdominal pain, jaundice, diarrhoea, and hormonal imbalances.
Chordoma	It is a rare type of bone cancer that typically occurs in the bones of the skull base or spine, arising from remnants of the notochord. Symptoms may include localized pain, neurological deficits, and problems with bladder or bowel function.
Burkitt Lymphoma	It is an aggressive type of non-Hodgkin lymphoma characterized by rapidly growing tumours in the lymph nodes, bone marrow, and other organs. It is associated with Epstein-Barr virus infection and typically presents with symptoms such as swollen lymph nodes, abdominal pain, and fever.
Adrenocortical Carcinoma	It is a rare and aggressive cancer that develops in the adrenal cortex, often causing hormonal imbalances and symptoms such as abdominal pain, weight loss, and high blood pressure.
RARE INFECTIOUS DISEASES	
Creutzfeldt-Jakob Disease (CJD)	It is a rare and rapidly progressive neurological disorder caused by abnormal prion proteins, leading to cognitive decline, involuntary movements, and eventually death within months to years of onset.
RARE PEDIATRIC DISEASES	
Batten Disease	It refers to a group of rare genetic neurodegenerative disorders affecting children, characterized by progressive loss of cognitive and motor function, vision impairment, seizures, and premature death. Also known as neuronal ceroid lipofuscinosis (NCL).
Neurofibromatosis Type 1	It is a genetic disorder causing tumours to grow on nerves throughout the body, leading to various complications such as skin changes, bone deformities, and neurological problems.
Alagille Syndrome	It is a rare genetic disorder affecting the liver, heart, and other organs, characterized by bile duct abnormalities, leading to liver damage and bile flow issues. Symptoms include jaundice, heart murmurs, and skeletal abnormalities.
Aicardi-Goutières Syndrome	It is a rare genetic disorder characterized by neurological and autoimmune symptoms, including progressive brain damage, abnormal brain calcifications, and elevated levels of interferon in the blood.

These are just a few examples, and there are many more rare diseases affecting people around the world. Each of these diseases presents unique challenges for patients and their families, including difficulties in diagnosis, limited treatment options, and the need for specialized care.

2. Orphan and rare diseases: Indian scenario

In India, the understanding and recognition of orphan and rare diseases have evolved over time. Historically, these diseases received little attention due to their low prevalence and the focus on more common health issues. However, awareness about rare diseases and the need for specialized care and support have been gradually increasing in India. It is difficult to develop orphan drugs due to inadequate financial and scientific resources and insufficient subjects to run clinical trials (6).

2.1 Early recognition

In the past, rare diseases were often misdiagnosed or undiagnosed in India due to limited awareness among healthcare professionals and the public. Many patients with rare diseases faced challenges in accessing appropriate medical care and support services

2.2 Emergence of patient's advocacy groups

Over the years, patient advocacy groups and non-profit organizations have played a crucial role in raising awareness about rare diseases in India. These organizations have worked to provide support, information, and resources to individuals and families affected by rare diseases, as well as advocating for better healthcare policies and funding for research and treatment.

2.3 Government initiatives

The Indian government has taken steps to address the needs of individuals with rare diseases. The National Policy for Treatment of Rare Diseases, launched by the Ministry of Health and Family Welfare in 2017, aimed to provide financial support for the treatment of rare diseases through the Rashtriya Arogya Nidhi (RAN) scheme. However, the implementation of this policy has faced challenges, including funding constraints and the need for clearer guidelines and criteria for eligibility.

2.4 Research and collaboration

Efforts to enhance research and collaboration in the field of rare diseases have been ongoing in India. Academic institutions, research organizations, and healthcare professionals have been involved in studies aimed at understanding the genetic basis of rare diseases developing diagnostic tools, and exploring potential treatments.

2.5 Challenges and opportunities

Despite progress, challenges remain in addressing the needs of individuals with rare diseases in India. These challenges include limited access to specialized healthcare services, high treatment costs, lack of awareness among healthcare professionals, and the need for better coordination and collaboration among stakeholders.

2.6 International cooperation

India has also participated in international collaborations and initiatives aimed at advancing research and treatment for rare diseases. Collaboration with global organizations, research institutions, and pharmaceutical companies has helped facilitate knowledge sharing, capacity building, and access to innovative therapies.

Overall, while significant strides have been made in recognizing and addressing the challenges of orphan and rare diseases in India, there is still much work to be done to ensure that individuals with rare diseases receive timely diagnosis, appropriate treatment, and comprehensive support. Continued efforts from all stakeholders, including government agencies, healthcare providers, patient advocacy groups, and the private sector, are essential to improving the lives of those affected by rare diseases in India.

A patient who suffers from rare diseases have an equal right to the medications as those who have common diseases. To follow tis and as per the National Policy on Rare Diseases, the Central Government provides financial support up to Rs. 15 lakhs under the Rashtriya Arogya Nidhi Umbrella Scheme for the treatment of rare diseases that need only one therapy.

3. Conclusion

The US-FDA has continuously made advances and improved the regulatory pathways after accepting the Orphan Drug Act, particularly, in clinical trials which have been successful in some cases. Recently, India has implemented regulations and policies that have impacted the ecosystem of rare diseases, which has long been neglected. According to WHO list of essential medicine, the proportion of orphan drugs in the essential medicine lists increased from 1.9 % (4 /208) in 1977 to 14.6% (70 /478) in 2021 (7). Orphan drugs constitute a unique class of pharmaceuticals in this sense since, in the absence of incentives and legislation pertaining specifically to orphan drugs, their development and marketing would not proceed.

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