NAVIGATING THE PROMISE LANDSCAPE OF UREA CYCLE DISORDER TREATMENT: AN IN-DEPTH EXPLORATION OF MARKET DYNAMICS AND GROWTH OPPORTUNITIES

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By

Deepali Gupta

Under the Supervision and Guidance of

Dr Neetu Purohit

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PharmaACE

Date: 28/06/2024

TO WHOMSOEVER IT MAY CONCERN

This is to certify that, **Deepali Gupta,** student of IIHMR University, Jaipur has completed her internship with **PharmaACE Analytics LLP** during the period of **April 01, 2024 to June 30, 2024.** During her internship she worked with the Competitive Intelligence department and has successfully worked on the project; **Navigating the promise landscape of Urea Cycle Disorder Treatment: An in-depth exploration of market dynamics and growth opportunities.**

We wish her every success in life.

Ashima Kumar

Ashima Kumar

Head – Training & Development and Corporate Communications

PharmaACE

DECLARATION

I hereby declare that this dissertation titled "Navigating the promise landscape of Urea Cycle Disorder Treatment: An in-depth exploration of market dynamics and growth opportunities" is the Bonafede record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

Deepali

(Signature)

Name of Student: Deepali Gupta

Date: 07/01/2024

IIHMR UNIVERSITY

CERTIFICATE

This is to certify that dissertation titled **NAVIGATING THE PROMISE LANDSCAPE OF UREA CYCLE DISORDER TREATMENT: AN IN-DEPTH EXPLORATION OF MARKET DYNAMICS AND GROWTH OPPURTUNITIES** is a record of the research work undertaken **by Deepali Gupta** in partial fulfillment of the requirements for the award of the degree of MBA Hospital and Health Management from the IIHMR University, Jaipur under my guidance and supervision and her approach to the research study has been sincere, scientific, and analytical.

Dr Neetu Purohit

IIHMR University, Jaipur

Date

Dr. Sanjay Gupta

IIHMR University, Jaipur

Date 03/07/2024

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ABSTRACT

Submitted by: Ms. Deepali Gupta Guided by: Dr Neetu Purohit

Roll No. 1491

Urea Cycle Disorder are very rare genetic disorders caused by deficiencies of certain enzymes of the urea cycle, which is responsible for the elimination of waste nitrogen from the organism in the form of urea. This would result in the accumulation of ammonia in the blood, generally very toxic when present in large amounts and possibly resulting in serious complications or even death if untreated. The ammonia scavengers are a class of drugs introduced to help remove excess ammonia in patients with UCD and other diseases associated with hyperammonemia,. The secondary data was collected from various clinical studies, journal articles, websites, and research articles. Value-wise, the US UCD treatment market is projected to be worth US$ 510.0 Mn in 2023 and is likely to witness a CAGR of 3.56% over the forecast period, 2023–2030. The prevalence of UCDs will increase with increasing population and growing life expectancy. Many novel drugs in the pipeline for UCDs, such as ammonia scavengers, are on their way to hit the market in upcoming years. According to the study, there is an incremental importance that ammonia scavengers portray in the treatment of UCDs. The growing prevalence of UCDs and the gaining acceptance of inorganic growth strategies by key players in the UCD market are likely to boost the growth of the market.

Keywords – Competitive intelligence, Urea cycle disorder, Ammonia scavengers, prevalence

CONTENTS

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Abbreviations

1. FDA- Food and Drug Administration- Federal Agency
2. CI- Competitive Intelligence
3. US- United States
4. CAGR- Compound Annual Growth Rate
5. R&D- Research and Development

Chapter 1 – Introduction

Urea Cycle Disorder are very rare genetic disorders caused by deficiencies of certain enzymes of the urea cycle, which is responsible for the elimination of waste nitrogen from the organism in the form of urea. This would result in the accumulation of ammonia in the blood, generally very toxic when present in large amounts and possibly resulting in serious complications or even death if untreated. The ammonia scavengers are a class of drugs introduced to help remove excess ammonia in patients with UCD and other diseases associated with hyperammonemia, such as liver disease urea cycle disorders using ammonia scavengers was conducted. Biochemical tests, genetic testing, and clinical signs are typically used to diagnose UCDs. However, newborn screening may be used to detect some forms. Alterations to one's diet, medications like sodium phenylbutyrate and glycerol phenylbutyrate, supplements, and, in severe cases, liver transplantation are all part of treatment strategies that aim to lower ammonia levels, provide alternative pathways for the excretion of nitrogen, and prevent episodes of acute hyperammonemia. This article aims to provide an overview regarding the current state of knowledge of the epidemiology of these UCDs, available treatments, and future drugs in the pipeline

1.1Ammonia Scavengers:

Ammonia scavengers are compounds that assist the body in getting rid of extra ammonia. These drugs are used to treat urea cycle disorders, which are hereditary conditions affecting the body's urea cycle-based ammonia removal capability. To help control high ammonia levels and avoid complications, ammonia scavengers can be used in conjunction with other treatments like a low-protein diet and amino acid supplements[1]

1.2 Classification of Ammonia Scavengers:

- Nitrogen-Scavenger Drugs: These drugs work by changing ammonia into a less harmful form that the body can eliminate through urine, thus removing it from the bloodstream. Benzoate and phenylacetate (PA)/phenylbutyrate (PB) are two examples.

- The ammonia scavenger glycerol phenylbutyrate is another one that is used to treat HE symptoms.
- Sodium Benzoate and Sodium Phenylacetate: These water-soluble substances are used to treat liver disease and urea cycle abnormalities by aiding in the removal of ammonia through the urine[1]

Chapter 2- Review of Literature

By conducting a comprehensive literature review on ammonia scavenger drugs market, one can gain a deeper understanding of the current landscape, identify gaps in knowledge, and highlight areas for further research or potential business opportunities

Table 2.1

S. No	Year of Publication	Article Title	Author Name	Description
1	2021	The burden of pharmacological treatment on health-related quality of life in people with a urea cycle disorder: a qualitative study	Gillian Yeowell, Danielle; Stephanie Burns & Francis Fatoye	According to this study, urea cycle disorders (UCDs), which are inborn errors in metabolism, can cause severe hyperammonaemia and consequently mortality or brain damage. Long-term care includes pharmaceutical therapy, restrictive protein consumption, and liver transplants in extreme cases. Pharmacological therapy such as sodium benzoate and sodium phenylbutyrate, while effective, have side effects such as gastrointestinal pain and foul taste. It has been shown that glycerol phenylbutyrate (GPB) has improved qualities and lessens part of the administration stress. In a research, nine parents of children with UCDs discussed the stress that a strict medication schedule caused them as well as the effects it had on their social lives. Making the transition to GPB helped to reduce some of the stress. but the illness's complications remained.(2)
2	2012	Suggested guidelines for the diagnosis and management of urea cycle disorders	Johannes Häberle, Nathalie Boddaert, Alberto Burlina,	Hyperammonaemia is the result of urea cycle disorders (UCDs), which are inborn errors of metabolism marked by abnormalities in the enzymes and transporters involved in the urea cycle. Poor results persist despite good interventions because of underdiagnosis and delayed diagnosis. Using a Delphi process, a trans-European consensus was created with recommendations for the diagnosis, treatment, and surveillance of UCDs. In order to improve results, the recommendations seek to standardize practices, establish consistent standards,

				and encourage awareness campaigns. One in 8,000 births is thought to be the approximate incidence of UCDs, and the condition is highly prevalent, with some cases going misdiagnosed until later in life. In order to avoid serious neurological injury and death, early diagnosis and treatment are essential, underscoring the need for greater public and healthcare professional awareness.(3)
3	2023	Genetic Therapy Approaches for Ornithine Transcarbamylase Deficiency	Berna Seker Yilmaz1 and Paul Gissen	The most prevalent urea cycle condition, ornithine transcarbamylase deficiency (OTCD), is typified by deficiencies in the ornithine transcarbamylase (OTC) enzyme. The *OTC* gene is mutated in this X-linked recessive condition, which affects men more often than women. Episodes of hyperammonemia are a hallmark of the disease, and if addressed, they can result in serious neurological problems and even death. Medication and dietary restrictions are part of the current treatment options, however they might not be enough to stop hyperammonemic episodes. The only treatment available, liver transplantation, is restricted because to the lack of available donors and the requirement for continuous immunosuppression. mRNA therapy, genome editing, and AAV gene insertion are a few of the strategies being investigated for gene therapy, which has demonstrated potential in tackling these issues. There are ongoing clinical trials and further developing these gene therapy techniques to raise their level of safety and effectiveness are future priorities(4)
4	2017	Glycerol phenylbutyrate for the maintenance treatment of patients with deficiencies in enzymes of the urea cycle	Nicola Longo & Robert Holt	Ammonia buildup is a hallmark of rare inborn metabolic abnormalities known as urea cycle diseases. During the past thirty years, various nitrogen excretion mechanisms have been utilized to increase lifespan and results. Sodium benzoate, phenylacetate, and phenylbutyrate are examples of early nitrogen scavengers that are successful in lowering ammonia levels, but they

				have side effects and administration problems that might restrict optimal outcomes and impair compliance. A pro-drug of phenylbutyrate called glycol phenylbutyrate was created to enhance treatment for patients suffering from problems related to the urea cycle. Glycerol phenylbutyrate research has yielded the most controlled study results in patients with urea cycle disorders, demonstrating that it is more tolerable than sodium phenylbutyrate while still allowing patients to meet their glutamine and ammonia objectives. Sustaining appropriate ammonia levels promotes improved long-term control and reduced neurological sequelae in patients with urea cycle defects.(5)
5	2024	Urea Cycle Disorder Market		A pipeline guide named "Urea Cycle Disorder Market," published by Global Markets Estimate, offers detailed information on treatments being developed for urea cycle disorder. The handbook examines the treatments' stages of development, pharmacological targets, modes of action, administration routes, and molecular kinds. It includes information about the treatments' pharmacological activity, history of research and development, and most recent news and press releases. The book also provides information on programs that have been shelved and reviewed important figures in the development of UCD therapies. It is anticipated that the market for Urea Cycle Disorder (UCD) would expand at a compound annual growth rate (CAGR) of 3.6% between 2023 and 2028. In 2023, the market is projected to grow to a value of USD 2.56 billion.The market is divided into segments based on area, route of administration, type of enzyme deficiency, and type of treatment. Due to the high prevalence of urea cycle diseases and the existence of major pharmaceutical companies involved in UCD, North America is anticipated to hold the highest share of the market. Because of the region's concentration of

				well-established pharmaceutical businesses and increased R&D spending, Asia Pacific is predicted to develop at the quickest rate. Among the leading companies in the industry are Recordati Rare Diseases, Eurocept Pharmaceuticals Holding, Bausch Health Companies Inc., and others.(6)

Objective:

- To extract information available for the marketed and available drugs for Urea Cycle Disorder
- To assess the potential of Ammonia Scavengers for Urea cycle disorder in US market
- To assess inline and pipeline drugs in US market.

Chapter 3 – Methodology

Type of Research: Secondary Research

Duration of study: 3 Months

Secondary Data was extracted from ct.gov website

Chapter 4 – Results

Information available for the marketed and available drugs for Urea Cycle Disorder

Oral Nitrogen Scavengers Available for Long-term Therapy[30,31,32]

The three most common nitrogen-scavenging medications employed for the chronic management of UCDs are as follows:

Nitrogen Scavengers for UCDs

Sodium benzoate - binds with glycine and forms hippuric acid, which is then excreted in the urine, hence resulting in an alternative pathway for nitrogen waste excretion1,3. It is metabolized to yield benzoic acid, and in an individual,

Sodium phenylbutyrate (NaPB) - Metabolised to phenylacetate, which then the liver and kidney forms phenylacetylglutamine. 80-100% of the drug is renally excreted within 24 hours as phenylacetylglutamine , NaPB demonstrated superior disposal of nitrogen than benzoate.

Glycerol phenylbutyrate (GPB)— GPB was non-inferior to NaPB for control of ammonia in clinical trials1.

These nitrogen scavengers provide alternative pathways for the excretion of waste nitrogen and work by bypassing the urea cycle. They are used in association with dietary protein restriction and supplementation with essential amino acids for the long-term management of UCDs.

	OLPRUVA™	**BUPHENYL®**	**RAVICTI®**	**PHEBURANE**	**CARBAGLU**
Indication:	Adjunctive therapy for the long-term care of adult and pediatric patients with UCDs with deficits in CPS, OTC, or AS who weigh 20 kg or more and have a BSA of 1.2 m2 or higher	Adjunctive therapy for the long-term care of UCD patients with AS, OTC, or CPS deficits. Every patient with a history of hyperammonae mia encephalopathy	Care of UCD patients on a long-term basis when dietary protein restriction and/or amino acid supplements are	Supplementary treatment to the standard of care for the long-term management of adult and pediatric patients with urea cycle disorders	Adjuvant therapy for acute hyperammonae mia brought on by a hepatic N-acetyl glutamate synthase (NAGS) deficiency. Treatment for c

		who has a condition with a neonatal onset. It must be used in conjunction with a low-protein diet and, occasionally, supplements containing vital amino acids	insufficient Use in conjunction with protein restriction in the diet and, occasionally, dietary supplements	(UCDs), involving deficits of CPS, OTC, or AS, and diet management	hronic hyperam monaemia caus ed by hepatic N - acetyl glutamate synthase insuffi ciency with mai ntenance therap y (NAGS).
Dosing	weighing at least 2 0 kg and having a BSA of at least 1.2 m2: 9.9– 13 g/m2/day	Those under 20 kg: 450– 600 mg/kg daily Individuals over 20 kg: 9.9– 13.0 g/m2/day	Patients unfa miliar with ph enylbutyrate between 4.5 a nd 11.2 g/m2/ day and 12.4 g/m2/day, wit h a maximum daily intake o f 17.5 ml.	Individuals und er 20 kg should take 450– 600 mg/kg of so dium phenylbut yrate every day. Individuals over 20 kg should ta ke 9.9– 13.0 g/m2/day o f sodium phenyl butyrate.	Adult and pedia tric patients wit h acute hypera mmonaemia sho uld receive dosa ges of 100– 250 mg/kg split into two to four doses, rounded t o the nearest 10 0 mg.
Formulation	2g, 3g, 4g, 5g, 6g, or 6.67g of NaPB s uspended orally	500 mg tablet fo rm;	(1100 mg/ml) liquid	NAPB in oral pellet form, 84 g.	200 mg of oral s uspension, funct ionally scored
Administrati on	3- 6 separate dosages while eating Every dosage is co ntained in a dosing envelope with one or two packets of NaPB for oral susp ension and one pac ket of suspending agent. Must be combined with the ready-made Mix- Aid suspension in 4 ounces of water; consume the full s uspension in 5 min utes to prevent coa	3- 6 evenly spaced doses each feedi ng powder; only oral administrati on (by mouth, g astrostomy, or n asogastric tube) is recommended .	3 (or higher f or patients un der the age of 2) dosages that a re split equall y with food or formula Administer wi th an oral syri nge straight in to the mouth. One may utili ze a gastrosto my or nasoga stric tube.	PHEBURANE dosing should b e scheduled to c oincide with me als. Measure the PH EBURANE oral pellets using th e calibrated dos age spoon. Eat the coated o ral pellets with a drink or mix th em with a teasp oon of pureed c arrot or apple sa uce. Avoid chewing PHEBURANE.	For an 80 mg/m L concentration, mix each 200 mg tablet with a t least 2.5 mL of water.

	ting dissolution; th en, rinse again wit h 4 ounces of wate r.			To reduce coatin g dissolution, s wallow right aw ay.	

Potential of Ammonia Scavengers for the indication Urea cycle disorder in US market

Key Players and Development [9,10]

The table below outlines the commercial availability and the market performance of these two ammonia scavenger drugs in treating UCDs in the United States. This gives a snapshot of what the current landscape has in store in terms of approved therapies against these rare genetic disorders The table below includes a pair of medicinal products approved FDA for the treatment of urea cycle disorders: RAVICTI (glycerol phenylbutyrate) and OLPUVA (sodium phenylbutyrate). These are thus ammonia scavengers that the excess amounts of ammonia in the body reduce—an important feature of UCDs.It captures, among others, drug name, drug class, company name, sales revenue for the United States, and the region where it has been approved. RAVICTI was developed by Amgen with $86 million in sales revenue in the US market, and the region approved is the US. OLPUVA, developed by Zevra Therapeutics, generated $27.5 million in sales in the US and has likewise been approved for use in the US.

Table 4.1

Drug name	Drug Class	Company Name	Sales Revenue (US)	Approval (Region)
RAVICITI	Ammonia Scavenger	Amgen	86Mn	US
OLPURVA	Ammonia scavengers	Zevra Therapeutics	27.5Mn	US

4.1 Urea Cycle Disorder Market Overview

The treatments for urea cycle disorders are expected to capture a USD 510.0 Mn market in 2023 and is likely to grow in the forecast period, 2023–2030, at a CAGR of 3.56%. The rising number of pipeline products and growing product approvals for the treatment of urea cycle disorders are factors that will probably boost the market growth during the projected period. Again, the growing acceptance by regulatory bodies of inorganic growth strategies of key players in the Urea Cycle Disorders Treatment market is likely to support the growth of the market in the United States during the projection period.

Key Pipeline therapies - US Market

Following are the steps used for extracting drugs in pipeline which are under clinical trials for treatment of Ura Cycle Disorder

a) Go to site Clinicaltrials.gov
b) Select Urea Cycle Disorder as disease/condition
c) Apply filters
d) In Recruitment: select all except suspended, terminated and withdrawn
e) In study type: Select Interventional
f) In funder type: Select industry
g) Download CSV/Excel format

Key pipeline for Urea Cycle Disorder

The pipeline for urea cycle disorders includes a number of promising drug candidates across various phases of development. These include the following:

1. DTX301 (Avalotcagene ontaparvovec): Ultragenyx Pharmaceutical has come up with gene therapy that replaces the deficient ornithine carbamoyl transferase enzyme. It is under Phase 3 clinical trials and involves the large-molecule infusion done intravenously.
2. AEB-1102 (Pegzilarginase) is in pre-registration for large molecule arginase replacement therapy and is being developed by Spyre Therapeutics. This agent is also delivered intravenously

3. ARCT-810: This large molecule therapy is under Phase 2 evaluation by Arcturus Therapeutics and works by inducing the expression of ornithine carbamoyl transferase. Administration is via intravenous infusion.

These pipeline drugs represent variety in therapeutic approaches, ranging from gene therapy to enzyme replacement and expression-stimulating mechanisms against underlying enzyme deficiencies in urea cycle disorders. A high phase of development for some of these candidates, such as DTX301 in Phase 3, most likely means good progress in expanding treatment options for patients with rare, life-threatening genetic conditions.

Table 4.2

Drugs in Pipeline	Molecule Name	Company	MOA	Development phase	Type of Molecule	ROA
DTX301	Avalotcagene ontaparvovec	Ultragenyx Pharmaceutical Inc	Gene transference; Ornithine carbamoyl transferase replacements	Phase 3	Large molecule	IV
AEB-1102	Pegzilarginase	Spyre Therapeutics	Arginase replacements	Pre-registration	Large molecule	IV
ARCT-810		Arcturus Therapeutics	Ornithine carbamoyl transferase expression stimulants	Phase 2	Large molecule	IV

4.1.1 Drivers:

Rising Number of Product approvals for urea cycle diseases. Increasingly, the products are gaining acceptance from regulatory bodies for the treatment of various urea cycle disorders, which is expected to boost market growth in the forecast period. The pharma companies Acer Therapeutics Inc. and Relief Therapeutics Holding AG, a commercial-stage biopharmaceutical company, collaborated to report in December 2022 that the FDA had permitted OLPRUVA for oral suspension. With this agreement, patients suffering from Urea Cycle Disorders-related deficits of Argininosuccinic acid synthetase, Carbamyl|phosphate synthetase, Ornithine Transcarbamylase are treated.7)

4.1.2 Market Contstraints:

The market for the treatment of Urea cycle jumble is held back by some factors, including:

a. High cost of therapeutics: The high cost of treatment for UCD is an access barrier to many patients. This would then result in either insufficient or delayed treatment of the condition, which may worsen and increase long-term healthcare costs.

b) Patient Non-Adherence: Being a complex condition, with the necessity for administering multiple medicines, treatment in most cases of UCDs is for life; hence, this could be a bit tricky to handle. It is among the topmost reasons for poor treatment outcomes and increased healthcare expenditure.

c) Restricted Admittance to Particular Care: UCDs call for particular consideration, which, in some areas, may be restricted. This could result in a delayed diagnosis and treatment, leading to an escalation of the condition, thereby increasing healthcare costs. d) Unawareness and Education Gap: Lack of education on part of healthcare providers about UCDs leads to late diagnosis and improper treatment. Such has negative consequences for the outcome and increases healthcare costs.

e) Limited access to effective therapies: Although there are several treatments available for UCDs, they do not work for all patients. This can trigger the absence of winning treatment alternatives for some patients, which makes their condition worse and increases healthcare costs.

f. Administrative Barriers: Administrative barriers, for example, admitting new drugs through lengthy endorsement procedures, impede the pace at which events unfold and affect the availability of effective treatments against UCDs. As a consequence, it might cause ineffective treatment options to patients that will only worsen the condition and increase healthcare expenses.

g) Inadequate Research and development: There is a lack of innovative work done in the area of UCDs that can result in the scarcity of effective treatment options and an lack of insight into the underlying causes about the condition. This may worsen the condition and increase healthcare costs.8

Urea cycle disorder treatment market for the U.S. is segmented based on various aspects to understand the details about the attributes shaping the growth of the market. They are:

a) Treatment Type

Medical Management (MM): Diet and Medication management to regulate ammonia levels.

a) Liver Transplantation: It means replacing the liver with a healthy one to regain the urea cycle function.

b) Type of Deficient Enzyme

• Ornithine Transcarbamylase Deficiency

• Arginosuccinate Synthetase Deficiency

• Arginosuccinate Lyase Deficiency

• Arginase Deficiency

• Hyperornithinaemia-Hyperammonemia-Homocitrullinuria Syndrome

• Citrullinemia Type II

c) Administration Route

• Oral

• Parenteral

d) Distribution Channel

• Hospital Pharmacies

• Retail Pharmacies

• Online Pharmacies

• Specialty Clinics

These segments help to understand the dissimilar treatment options, specific enzyme deficiencies, and diverse ways in which treatments are administered and distributed within the U.S. market for urea cycle disorders.7

Urea Cycle Disorder is a life-threatening buildup of ammonia in the blood that can cause brain damage, coma, and even death if left untreated. Urea cycle disorders (UCDs) are a group of rare genetic conditions caused by deficiencies in enzymes involved in the urea cycle.

Biochemical tests, genetic testing, and clinical signs are typically used to diagnose UCDs. However, newborn screening may be used to detect some forms. Alterations to one's diet, medications like sodium phenylbutyrate and glycerol phenylbutyrate, supplements, and, in severe cases, liver transplantation are all part of treatment strategies that aim to lower ammonia levels, provide alternative pathways for the excretion of nitrogen, and prevent episodes of acute hyperammonemia. People who have these rare but serious genetic disorders should get a diagnosis as soon as possible and get treatment right away if they want to avoid catastrophic outcomes and have better long-term outcomes[11]

4.2.1 The UCD Subtypes [12,13]

Urea cycle disorders are categorized into subtypes according to the enzyme deficient in each type. There are a total of six subtypes of urea cycle disorders:

OTCD : This is the most common UCD and is caused because of the deficit of the OTC enzyme. It is the only X-linked UCD, meaning males are more severely affected than females:

Carbamoyl phosphate synthetase I deficiency: due to a deficiency of CPS1 enzyme. The symptoms in the severe neonatal form appear 24-72 hours after birth as described first.

Argininosuccinate synthetase deficiency(citrullinemia type 1): caused by a deficiency of the ASS enzyme and very high levels of citrulline.

Argininosuccinate lyase deficiency (argininosuccinic aciduria): due to ASL enzyme deficiency. The neonatal form is severe, and presents within 24-48 hrs .

Arginase 1 deficiency: the most rare UCD, resulting from ARG1 enzyme deficiency .

N-acetylglutamate synthase deficiency: the most severe UCD, caused by NAGS enzyme deficiency .

The other subtypes include hyperornithinemia-hyperammonemia-homocitrullinuria syndrome and citrullinemia type 2. Inheritance for all of the UCDs except OTC is autosomal recessive.

The severity depends on the particular enzyme deficiency, but generally proximal defects, like NAGS and CPS1, are more severe than distal defects[3]. Complete enzyme deficiencies typically present in neonates with hyperammonemic crises, while partial deficiencies present at any age and their presentations vary.

Table 4.3

	Disease	**Causal Gene**	**Inheritance**
Proximal Urea Cycle Defect	NAGS Deficiency	NAGS	Autosomal recessive
	CPS1 Deficiency	CPS1	Autosomal recessive
Distal Urea Cycle Defect	OTC Deficiency		X- linked
	ASS Deficiency		Autosomal Recessive
Transporter Defect	HHH Syndrome (ORNT1D)	SLC25A15	Autosomal Recessive
	Citrin Deficiency	SLC25A13	Autosomal Recessive
	ARG Defeciency		Autosomal Recessive

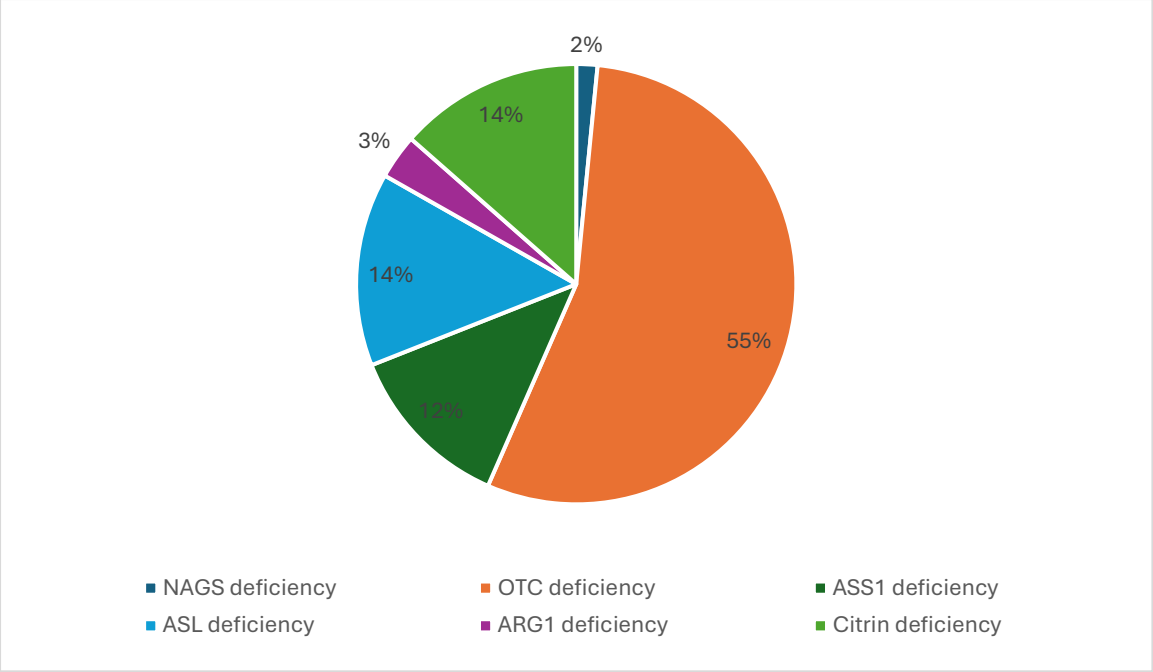
4.2.2 Incidence and Prevalence [14,15,16]

The estimated frequency of UCDs in the United States is probably on the order of 1 in 35,000 births. However, given that many cases are undiagnosed, especially milder forms that present later in life, the real incidence might be much higher. The number of cases identified has increased obviously through newborn screening programs. Continual efforts at increasing awareness and screening will be required to develop a better understanding of the epidemiology of these life-threatening, rare metabolic disorders in the US.

Incidence of UCD subtypes	
OTCD	1:56,500

ASLD	1:218,750
ASSD	1:250,000
ARGD	1:950,000
CPS1D	1:1,300,000
NAGSD	<1:2,000,000
HHH	<1:2,000,000
CITRIN	<1:2,000,000

Fig 4.1: Incidence of different types of UCD



Urea Cycle Disorder Consortium

About 1 in 56,500 people have ornithine transcarboxylase deficiency (OTCD), which is the most prevalent UCD. The incidence of arginosuccinate lyase deficiency (ASLD) is 1 in 218,750, whereas the incidence of arginosuccinate synthase deficiency (ASSD) is 1 in 250,000. One in 950,000 people have arginase deficiency (ARGD), while one in 1,300,000 people have carbamoyl phosphate synthetase I deficiency (CPS1D). Less than 1 in 2,000,000- people suffer with N-acetyl glutamate synthase deficiency (NAGSD), Citrine deficiency (CITRIN), and hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (HHH).(15.16)

4.2.3 Pathophysiology:

The pathophysiology of urea cycle disorders (UCDs) involves a defect in the urea cycle, which is a critical metabolic pathway that converts ammonia into urea, a water-soluble compound that can be excreted by the body. The urea cycle is a complex process that involves several enzymes and transporters, and defects in any of these components can lead to UCDs.

The urea cycle begins with the conversion of ammonia and carbon dioxide into carbamoyl phosphate, which is then converted into citrulline. Citrulline is then converted into arginosuccinate, which is eventually broken down into arginine and fumarate. Arginine is then converted into urea and ornithine. The urea cycle is a critical process that helps remove ammonia from the body and maintain normal blood ammonia levels.

Key Points

- Defects in Enzymes and Transporters: UCDs are caused by defects in six enzymes and two transporters that are involved in the urea cycle. These enzymes include carbamoyl phosphate synthase I (CPS I), ornithine transcarbamylase (OTC), argininosuccinate synthase (ASS), argininosuccinate lyase (ASL), arginase, and $$N$$-acetylglutamate synthetase (NAGS). The transporters involved are ornithine transporter and citrulline transporter
- Hyperammonemia: An excess of ammonia in the blood is known as hyperammonemia and is the main feature of UCDs. Ammonia is harmful to the body and, depending on the degree of hyperammonemia, can result in a variety of symptoms, ranging from minor to severe.

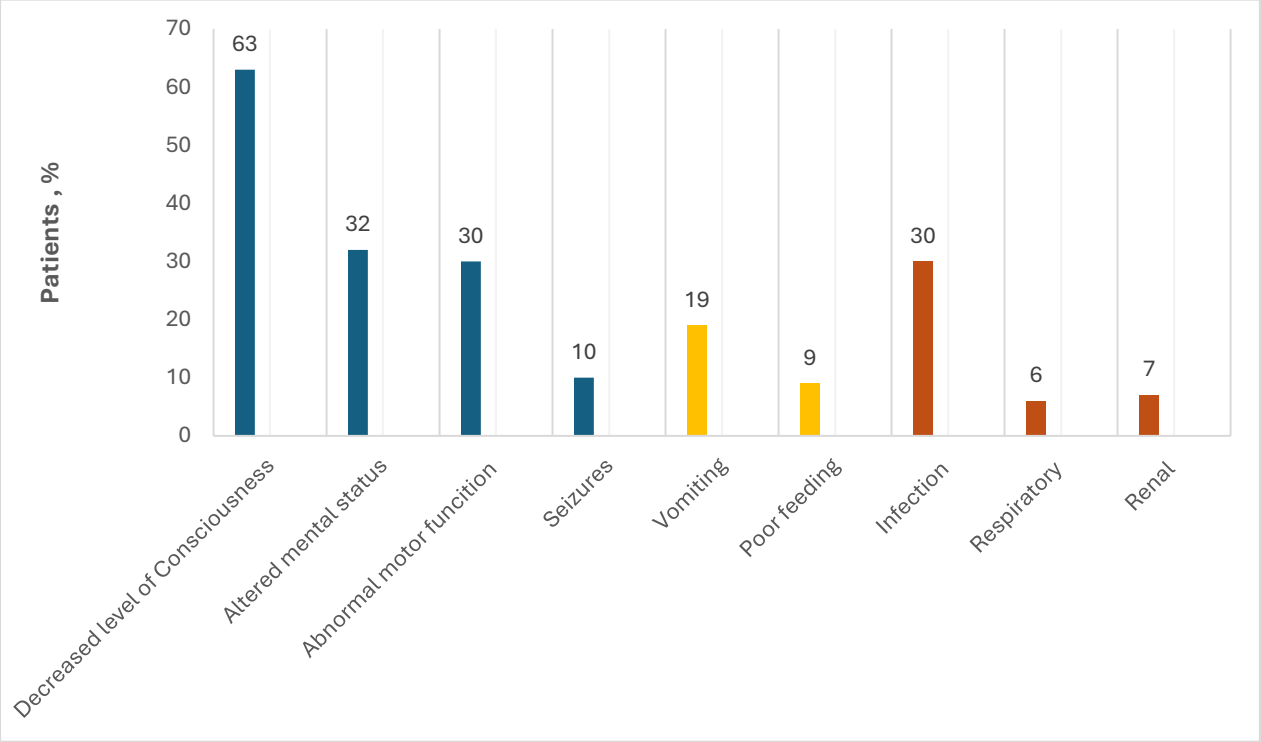
4.2.4 Symptoms

Symptoms of UCDs include vomiting, headaches, aggression, lethargy, and seizures. In severe cases, hyperammonemia can lead to a hyperammonaemia crisis, which can cause coma, brain damage, or even death

Inheritance Patterns:

All UCDs are inherited in an autosomal recessive form, with the exception of X-linked OTC deficiency. This indicates that for a child to be affected by the disorder, they must inherit two copies of the defective gene, one from each parent (17).

Fig 4.2 : Symptoms occurring in > 5 % of patients at first episode



Data based on 260 patients with confirmed diagnosis of a UCD who were treated for 975 episodes of h0spitalization between 1982 and 2003.

Patients with urea cycle disorders (UCDs) who were experiencing hyperammonaemia crises were the subjects of the extensive longitudinal interventional study. Somewhere in the range of 1982 and 2003, information was gathered on 260 patients getting intravenous nitrogen rummaging drugs (Ammonul) for the treatment of hyperammonaemia episodes brought about by UCDs, addressing 975 hospitalization episodes. As opposed to assumptions, just 34% of these patients introduced inside the initial 30 days of life, with a death pace of 32% in this neonatal beginning gathering. The greater part (66%) of patients had late-beginning introducing issues and displayed delayed endurance contrasted with the neonatal-beginning gathering. Neurological (80%) or gastrointestinal symptoms were the most common presenting symptoms. This companion addresses the biggest assortment of UCD patients revealed in the US, giving significant experiences into the normal history and clinical show of these uncommon hereditary issues.(18)

Characteristics of Early-Onset Versus Late-Onset UCDs

The main distinction is that early-onset UCDs are associated with more severe genetic mutations and enzyme deficiencies, leading to a rapid accumulation of ammonia shortly after birth. In contrast, late-onset UCDs involve milder genetic changes that allow some enzyme function, but hyperammonemia can still occur during times of metabolic stress. Prompt diagnosis and treatment are critical to prevent brain damage in both forms of UCDs.

Table 4.4

Early-onset UCDs	**Late-onset UCDs**
Gene deletions, nonsense mutations, frameshift mutations	Missense mutations
Complete or near-complete enzyme deficiency	Partial enzyme deficiency
Within days, infants exhibit the warning signs and symptoms of hyperammonemia.	The first clinical episode may not be identified for several months or even years.
-	Stress or a severe sickness can cause ammonia to build up at any time in life.
-	Less severe hyperammonaemia has subtler symptoms.(19)

The Clinical Spectrum of UCDs Varies Widely

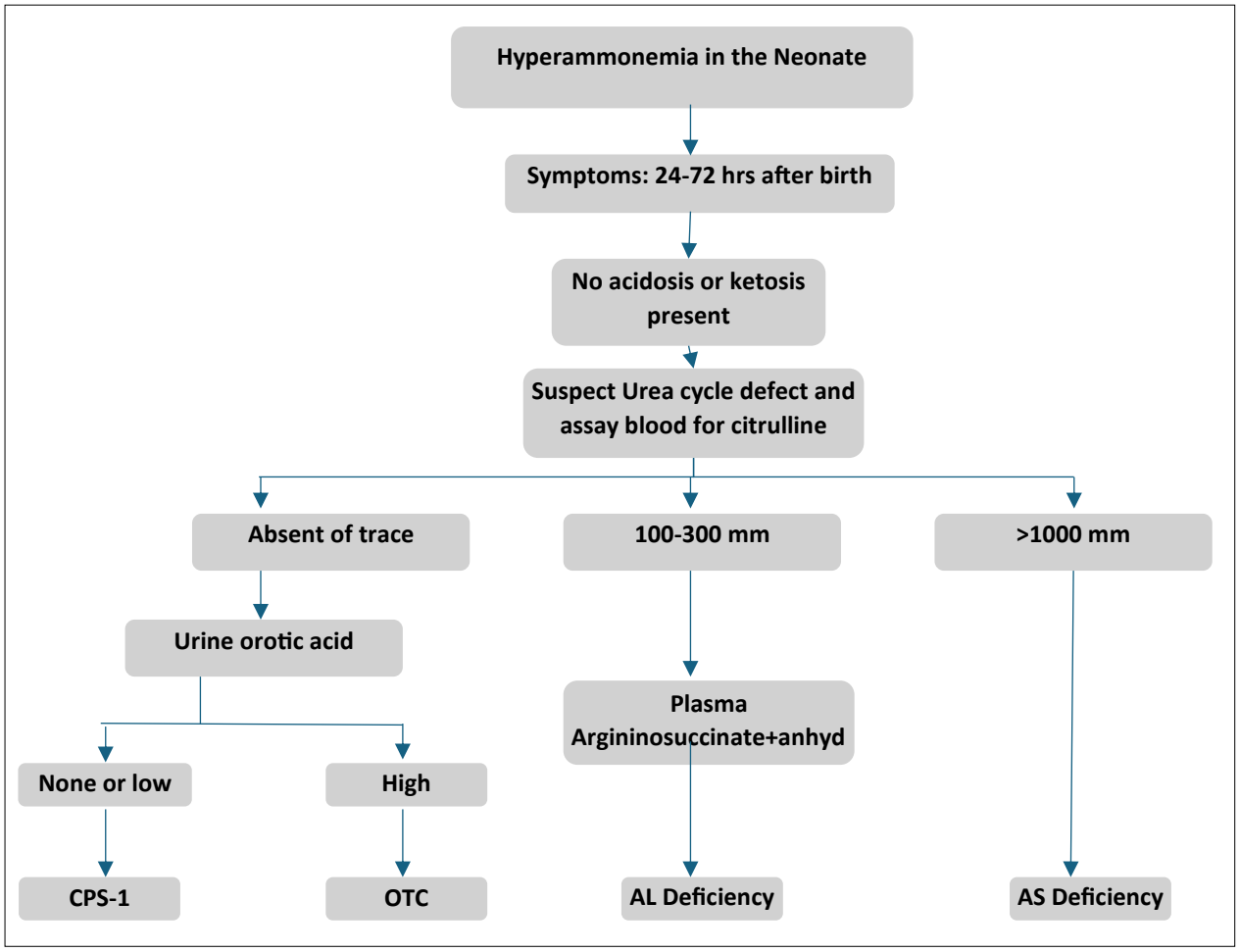
The early-onset UCDs are characterized as being normal in appearance at birth and having a gradual, acute, and dramatic rise in nitrogen load, associated with somnolence, lethargy, and eventually coma. Furthermore, affected infants can demonstrate loss of thermoregulation in the form of hypothermia, neurologic posturing from cerebral edema, and rapid decline in neurologic status. Affected infants may also have loss of thermoregulation in the form of hypothermia, neurologic posturing due to cerebral edema, and rapid decline in neurologic status. On the contrary, late-onset UCDs have signs and symptoms that include subtle

avoidance of dietary protein, history of behavioral and psychiatric problems, disruption of feeding that results in more catabolism, and acute encephalopathy not explained by specific disease. Cerebral edema can be appreciated in radiography in late-onset cases, which can also be associated with seizures, hyperventilation followed by hypoventilation, reduced oral intake before decompression.

One key difference is that early-onset UCD results from a complete or near-complete enzyme deficiency, which rapidly accumulates ammonia and causes acute neurological symptoms, while the late-onset cases with partial enzyme deficiency permit some function but still give rise to hyperammonemic crises precipitated by metabolic stress. Diagnosis and treatment should therefore be swift in order to prevent brain damage and long-term complications of the disorder.

Early-onset UCDs	**Late-onset UCDs**
Normal appearance at birth	Abrupt and dramatic rise in nitrogen load following trauma, abrupt loss of weight, or accelerated protein turnover following intravenous steroids
Sleepiness leading to fatigue and finally a coma	Avoidance of dietary protein
Loss of thermoregulation (hypothermia)	History of behavioural or psychiatric illnesses
Feeding disruption (increases catabolism)	Rapid deterioration of neurologic status
Neurologic posturing (from cerebral edema)	Severe encephalopathy that is not consistent with a disease Radiography or a clinical evaluation showing signs of cerebral edema
Seizures	Seizures most of the time
Hyperventilation, followed by hypoventilation	Reduction in oral intake prior to decompensation (20)

Fig 4.4 Diagnosis of UCD



4.2.5 Diagnosis

The following are crucial steps in UCD diagnosis:

a) **Plasma amino acid profile:** Elevated concentrations of amino acids can be used to determine the presence of an enzyme deficiency

- Increased ornithine suggests an OTC or CPS1 deficit.
- ASS1 deficiency, or citrullinemia, is indicated by elevated citrulline.
- ASL deficiency, or argininosuccinic aciduria, is indicated by elevated arginosuccinate.
- ARG1 deficiency, or arginase deficit, is indicated by elevated arginine.

b) **Analysis of urine organic acid:** High amounts of orotic acid can aid in differentiating between OTC and CPS1 deficiencies.

c) **Genetic testing:** By pinpointing the precise gene mutation causing the UCD, genetic analysis helps validate the diagnosis.

d) **Ammonia levels:** A hallmark of UCDs is hyperammonaemia, or increased blood ammonia, which can be utilized to confirm the diagnosis.

Genetics, Clinical and Biochemical Presentation, and Diagnostic Tests for UCDs[12]

The most common subtype is ornithine transcarbamylase deficiency, inherited in an X-linked pattern; all the other UCDs have autosomal recessive inheritance. Probably, the majority of patients have very variable symptomatology, with extremes of severe, neonatal-onset hyperammonemic crises and subtle late-onset neurologic and psychiatric symptoms. Classic cases are those involving complete or near-complete deficiency in enzyme activity, most frequently seen in early onset cases, resulting in rapid accumulating toxic ammonia. In late-onset cases, this is usually a partial deficiency in enzyme activity. The diagnosis combines clinical symptoms with biochemical results of increased ammonia, glutamine, and orotic acid levels, besides genetic tests that allow the identification of the disease-causing genetic mutation. Diagnosis and treatment are crucial to avoid life-threatening complications and long-term neurological damage in patients with UCDs.

Table 4.6

UCD Subtype	Inheritance	Casual Gene	Clinical Manifestations	Biochemical Markers	Diagnostic Test
NAGSD	Autosomal recessive	NAGS	Encephalopathy, neurobehavioral	HA, ↑ plasma glutamine, low citrulline	DNA
CPS1D	Autosomal recessive	CPS1	Encephalopathy, neurobehavioral	HA, ↑ plasma glutamine, low citrulline	Liver enzyme analysis; DNA
OTCD	X-linked	OTC	Encephalopathy, neurobehavioral, liver disease (infrequently)	HA, ↑ plasma glutamine, low citrulline, ↑ urine orotic acid	DNA, liver enzyme analysis
ASSD	Autosomal recessive	ASS1	Encephalopathy, neurobehavioral	HA, ↑ plasma citrulline	Fibroblast enzyme

					analysis, DNA
ASLD	Autosomal recessive	ASL	Encephalopathy, neurobehavioral, liver disease (frequently), trichorrhexis nodosa	HA, ↑ plasma citrulline, and argininosuccinic acid	Fibroblast enzyme analysis, DNA
ARGD	Autosomal recessive	ARG1	Spastic diplegia, neurobehavioral	Increased plasma arginine, t urine orotic acid	Red blood cell enzyme analysis
HHH	Autosomal recessive	SLC25A15	Encephalopathy, neurobehavioral, spastic diplegia, retinal disease	HA, ↑ plasma ornithine, t urine homocitrulline, ↑urine orotic acid	Fibroblast incorporation assay, DNA
CITRIN	Autosomal recessive	SLC25A13	Neuropsychiatric, neonatal cholestatic hepatitis	HA, ↑ plasma citrulline, and arginine	DNA

4.2.6 Different modes of diagnosis for UCD's

Newborn Screening and Differential diagnosis:

A blood test that gauges the baby's blood's concentrations of specific amino acids and other chemicals is usually used to screen newborns for UCDs. Usually, this screening is carried out in the initial days following delivery, before the infant exhibits any symptoms. The sensitivity and specificity of screening for ASS1 and ASL insufficiency differ by state, however current newborn screening panels in the US that use tandem mass spectr0metry detect aberrant quantities of analytes associated with both illnesses in all states.

- Fl0rida, Maine, Massachusetts, Mississippi, New Hampshire, Pennsylvania, Rhode Island, and Vermont screen for CPS1 deficiency.
- OTC deficiency is likely to be found in Kentucky and Utah and is screened for in Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont.
- Thirty-five states screen for agluinase deficiency.

- Four more states are likely to detect it. 36 states screen for citrin deficiency, and 13 additional states are likely to detect it.

Furthermore, even in cases where UCDs are identified through newborn screening, newborns frequently exhibit symptoms before the findings of the screening are available. Consequently, healthcare practitioners must have a high degree of clinical suspicion.

Prenatal examinations: In addition to helping with perinatal care, prenatal analysis can show whether milder UCDs are present. Prenatal testing requires a consultation with clinical geneticists and metabolic specialists. The preferred method for reliably identifying UCDs, providing genetic counselling, and, in certain situations, forecasting prognosis is mutation analysis.
DNA-based mutation analysis for CPS1D disease from CVS or AFC is one example of this testing.

Genetic testing at the molecular level: Molecular genetic testing is the primary diagnostic technique utilized to accurately detect and confirm all UCDs. For each of the eight UCDs, molecular genetic testing is the preferred prenatal technique. This approach replaces the examination of enzyme activity as a trustworthy diagnostic technique. It considers genome sequencing, exome sequencing, and single and multi-gene testing.
Assay for Enzyme Activity :An effective technique for identifying UCDs in uninformative molecular genetic testing is the enzyme activity assay.
Enzyme activity can detect most illnesses and can be useful if estimation based on DNA is not acceptable. Enzyme activity assays use erythrocytes, intestinal mucosa, fibroblasts, and liver tissue to diagnose UCD if molecular testing is unable to do so (22)

4.2.7 Treatment Management for UCD

Acute Treatment of UCDs: source bookmarked

To prevent brain damage and other complications, acute treatment of urea cycle disorders (UCDs) focuses on rapidly lowering blood ammonia levels.
The primary objectives are:

- Get rid of the ammonia in the blood.

- Feed protein with calories and nutrients to prevent its breakdown
- Forestall further alkali creation

Key parts of intense therapy include:

- Dialysis In adults with acute decompensations, first-line treatments for quickly removing ammonia from the blood include hemolysis or continuous veno-venous hemofiltration Dialysis is continued until the patient is clinically better and ammonia levels are stable.
- Injectable Fluids IV liquids containing glucose and lipids are given to give calories and forestall catabolism, which would somehow or another increment alkali creation from protein breakdown

Treatments Meds like sodium benzoate and sodium phenylbutyrate tie to amino acids to work with smelling salts discharge in urine. Supplementing with arginine or citrulline can support the urea cycle and assist in the elimination. of ammonia

Limitations on Dietary Protein Dietary protein is confined to restrict smelling salts creation from amino corrosive metabolism. However, to stop catabolism, it is necessary to provide enough calories from fats and carbohydrates.

Checking To guide treatment and prevent complications, frequent monitoring of blood ammonia, electrolytes, acid-base status, and nutritional parameters is essential.
Neuroimaging might be utilized to survey cerebral edema. Many patients can survive acute hyperammonemia crises with prompt diagnosis and aggressive treatment. Notwithstanding, long haul results rely upon the particular UCD, period of beginning, and level of cerebrum injury preceding diagnosis. For some UCDs, liver transplantation may be an option.(23)

Pharmacologic treatment:

Urea cycle disorders (UCDs) have several important pharmacologic treatments, including:

- Nitrogen-searching meds Sodium phenylbutyrate and sodium benzoate bind to the amino acids glycine and glutamine, respectively, to facilitate their excretion in the urine and

eliminate excess nitrogen. These drugs aid in the reduction of blood ammonia levels and the prevention of hyperammonaemia crises.

- Taking citrulline or arginine supplements Adding urea cycle intermediates like arginine or citrulline can help the urea cycle incorporate more nitrogen. Arginine is a positive controller of N-acetyl glutamate, a fundamental cofactor for the urea cycle compound carbamoyl phosphate synthetase
- Oral citrulline may be more effective than arginine, according to studies, especially in patients with ornithine transcarboxylase (OTC) deficiency.
- Liver replacement surgery Since the liver is the primary location where urea cycle enzymes are produced, liver transplantation may be an option for some severe, treatment-refractory UCDs.
- The type of UCD, its severity, the patient's age, and their clinical condition all influence the specific pharmacologic treatment plan. Meds are utilized in mix with dietary protein limitation and other strong measures to deal with these perplexing, hazardous disorders. (2)

Chronic Management:

- Nutrition

Principles of Long-Term Management of UCDs

The following are the fundamental tenets of long-term treatment for urea cycle disorders (UCDs):

a) Dietary Control: Long lasting protein-confined diet to restrict nitrogen/alkali creation . Supplementation with fundamental amino acids like arginine or citrulline to help the urea cycle

b) Regular checking of development, dietary status, and biochemical markers

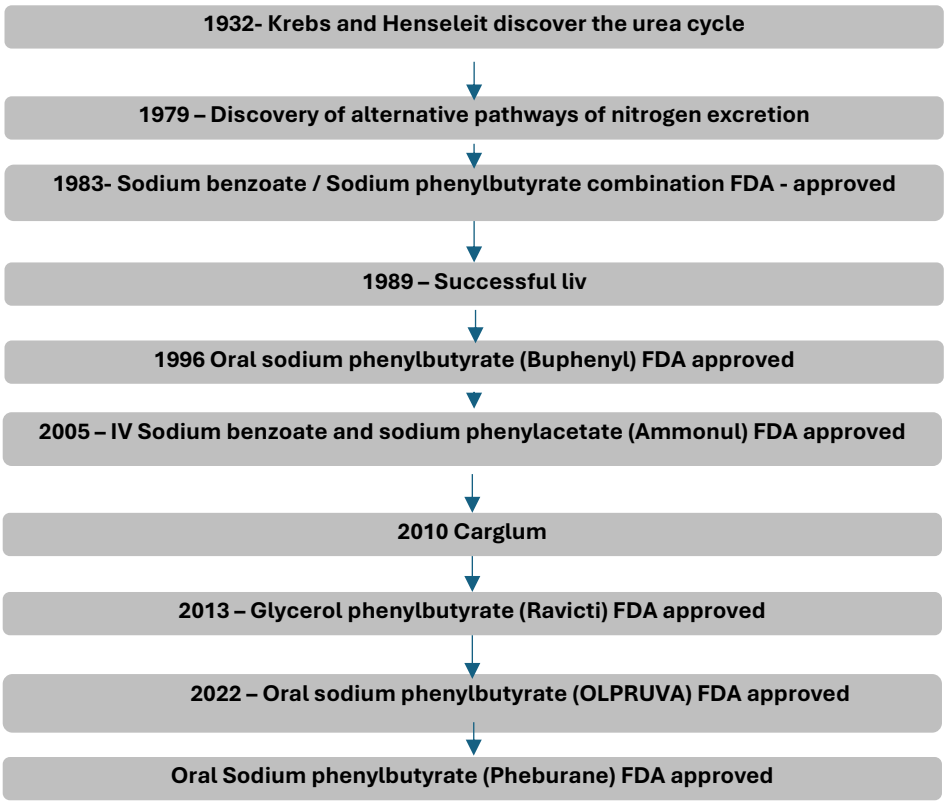
c) Pharmacologic Treatment: Utilization of nitrogen-searching prescriptions like sodium benzoate or sodium phenylbutyrate to work with alkali discharge. Taking arginine or citrulline supplements to improve the function of the urea cycle In severe cases where treatment has failed, liver transplantation may be considered.

d) Checking and Preventive Consideration: Regular blood tests to screen alkali, amino acids, and other metabolic boundaries. Quick treatment of concurrent diseases or other catabolic stressors can set off hyperammonemic crises. Formative, neuropsychological, and instructive appraisals to distinguish and address any mental or useful shortfalls . Assistance with family planning and genetic counseling

e) Coordination of Care across the Board Collaboration among metabolic specialists, dietitians, neurologists, developmental pediatricians, and other professionals in allied health .Arrangement of strong administrations like physical, word related, and language training depending on the situation

f) Propaganda for the right school accommodations and resources from the community maintaining metabolic stability, avoiding acute decompensations, and maximizing growth, development, and quality of life for individuals with these rare, life-threatening disorders are the primary objectives of chronic management. For the best possible outcomes, it is essential to adhere to the treatment plan throughout one's life.(24)

Fig 4.5 Chronic Management: Pharmacologic Treatments[25.26.27.28.29.30]



Considerations for Liver Transplantation in UCD

Due to its ability to correct the metabolic deficit and eliminate the risk of hyperammonemia, liver transplantation (LT) has emerged as a promising treatment option for urea cycle disorders (UCDs)

Notwithstanding, LT is a complex surgery that conveys dangers of mortality, bleakness, and requires long lasting immunosuppression. The choice to seek after LT in UCD patients depends on a few variables:

The extent of UCD: Candidates for LT are more likely to be patients with severe UCDs who do not respond adequately to standard medical treatment. In one review, all overcomers of the neonatal-beginning type of UCD got LT, while 73% of females with OTC lack and 59% of patients with late-beginning structures went through LT.

Metabolic Decompensations that recur in order to prevent further neurological damage, patients with recurrent hyperammonemic episodes that necessitate hospitalization are considered for LT

Standard of Living: UCD patients whose quality of life is poor due to the burden of dietary restrictions, medications, and frequent hospitalizations are considered for LT.

Neurological Status: LT is commonly suggested for UCD patients without extreme prior neurological harm, as it can't turn around laid out neurological deficits .

Individual Variables: Each patient's decision regarding LT is based on factors such as preventing neurological damage, metabolic stability, and age.

Timing of LT: Ideally, LT is started when patients' metabolic stability is stable, not when they are in an acute hyperammonemic crisis. In synopsis, the equilibrium between dangers and advantages of LT should be painstakingly weighed for each UCD patient, especially in gentle to-respectably impacted individuals. As careful results keep on improving, LT is turning into an undeniably suitable choice to forestall neurological difficulties and work on personal satisfaction in fittingly chosen UCD patients.(33)

Tipping point in decision influenced by multiple factors

- Disease severity
- Disease stability
- Burden on child/family
- Physician approach
- Consideration for child's independence

Table 4.8

Benefits	Limitations
Potentially curative	Does not reverse neurological damage
Normalizes ammonia levels	Risk of morbidity and mortality
Improves QoL	Life-long immunosuppression
Allows for normal diet	Defective enzymes remain in other organs

4.3 UCD Market Drivers

Treatment for urea cycle disorders are expected to grow at a compound annual growth rate (CAGR) of 3.56% in the United States between 2023 and 2030, reaching a value of US$ 510.0 million in 2023. Market growth is anticipated to be fueled by an increasing number of products in the pipeline and product approvals for urea cycle disorders. Additionally, major players in the Urea Cycle Disorders Treatment market are anticipated to fuel the market's expansion in the United States during the forecast period due to regulatory agencies' growing acceptance of inorganic growth strategies.(7)

US Market for the Treatment of Urea Cycle Disorders:

Factors influencing the rise in urea cycle disease product approvals The approval of products by regulatory bodies for the treatment of urea cycle disorders is expected to drive market expansion over the projected period. The pharmaceutical companies Acer Therapeutics Inc. and Relief Therapeutics Holding AG, a commercial-stage biopharmaceutical business, worked together to announce in December 2022 that the FDA had authorized OLPRUVA (sodium phenylacetate) for oral suspension. With this approval, patients with urea cycle disorders

(UCDs) involving deficits in argininosuccinic acid synthetase (AS), carbamy|phosphate synthetase (CPS), ornithine transcarbamylase (OTC) will be treated.(7)

Table 4.9

Active Ingredient	Company	Brand Name	Dosage form	Route	Strength	Approval date
Glycerol Phenylbutyrate	Horizon	RAVICTI	Liquid	Oral	1.1 GM/ML	2013
Carglumic Acid	Recordarti Rare Diseases	CARBAGLU	Tablet, for Suspension	Oral	200MG	2010
Sodium Phenylbutyrate	Acer Therapeutics	OLPRUVA	For Suspension	Oral	2GM/3GM/4/GM/5GM/6GM/6.67GM Packet	2022
	Medunik USA	PHEBURANE	Pellets	Oral	84GM / BOT	2022
	Horizon	BUPHENYL	Powder	Oral	3GM / TEASPOONFUL	1996
			Tablet	Oral	500MG	1996
Sodium Phenylacetate &Sodium Benzoate	Bausch Health	AMMONUL	Injection	IV	10%/10%	2005

4.4 Limitations

The study is done based on the limited available data that is available on open sources

Chapter 5 : Conclusion

Ammonia scavenger drugs are commonly used to treat urea cycle disorder and have other therapeutic uses as well. Between 2023 and 2030, the United State treatment market for urea cycle disorders is projected to expand at a compound annual growth rate (CAGR) of 3.56%, reaching a value of US$ 510.0 million in 2023. A rising number of medications in the pipeline and product approvals for urea cycle diseases are expected to drive market expansion. Furthermore, because regulatory bodies are beginning to allow inorganic growth techniques, key players in the Urea Cycle Disorders Treatment market are expected to drive the market's rise in the United States throughout the forecast period.

Urea cycle disorder affects approximately 1 in 35000 people of the population and is expected to become more common in future as the world population increases and people live longer. The highest prevalence of urea cycle disorders (UCDs) is seen in late-onset cases, which account for 69% of patients

The global market offers various drugs for treatment of UC, including ammonia scavengers but there are certain key unmet needs in UCD treatment which needs to be addressed that includes high costs, poor patient adherence due to side effects, lack of therapies for negative and cognitive symptoms, delayed diagnosis, and limitations of liver transplantation

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