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Mini Review

Thalidomide Pharmacological Actions of a Banned Drug

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ABSTRACT

Thalidomide, originally introduced in the late 1950s as a sedative and treatment for morning sickness in pregnant women, became infamous for causing severe birth defects. Though banned in many countries, it re-emerged in later decades for specific indications such as multiple myeloma and leprosy-associated complications. This review provides a comprehensive overview of its history, pharmacology, adverse effects, regulatory actions, and current therapeutic repositioning. The article highlights lessons learned and the evolution of drug safety protocols shaped by the thalidomide tragedy. Thalidomide is an infamous pharmaceutical agent once marketed as a safe sedative and antiemetic, particularly for pregnant women. Its widespread use in the late 1950s and early 1960s led to a global tragedy when it was found to cause severe congenital malformations, most notably limb deformities (phocomelia), in thousands of newborns. The thalidomide disaster triggered sweeping reforms in drug development, testing, and regulatory oversight, with long-standing impacts on patient safety and pharmaceutical policy worldwide. Despite its notorious history, thalidomide has found renewed medical applications in the treatment of conditions such as multiple myeloma and leprosy, but with strict precautions to avoid fetal exposure. This review summarizes the history, mechanisms of harm, regulatory changes, and current clinical status of thalidomide, highlighting its lasting legacy on medicine and drug safety.

INTRODUCTION

Thalidomide represents one of the darkest chapters in pharmaceutical history. Marketed initially as a safe sedative for pregnant women, its teratogenic effects were devastating. By the early 1960s, over 10,000 children worldwide were born with severe malformations due to prenatal exposure to thalidomide [1]. Despite its ban, the drug has seen a resurgence in controlled medical settings. This review explores the dual life of thalidomide from tragedy to therapeutic potential.

2.History and Development

- **Development and Marketing:** Thalidomide was first developed by CIBA (Switzerland) in

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1953 and introduced by the German company Chemie Grünenthal in 1956, under various brand names including Contergan. It was used widely in Europe and other regions for anxiety, insomnia, and particularly as a treatment for *morning sickness* in pregnant women.

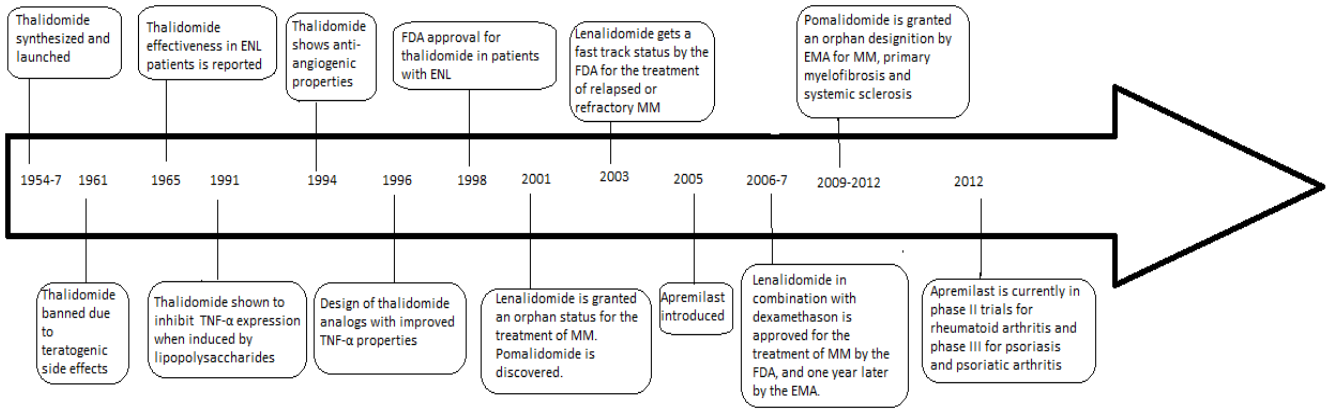
- **Lack of Testing:** At the time, drug safety evaluations did not require testing for teratogenic effects. Thalidomide was deemed nontoxic based on animal studies, which failed to reveal its risks to human embryos.

The Scandal and Ban

- **Discovery of Side Effects:** In 1961, Dr. William McBride (Australia) and Dr. Widukind Lenz (Germany) linked thalidomide use during pregnancy to congenital malformations, most notably limb deformities such as phocomelia (malformed or absent limbs).

- **Global Impact:** Estimates suggest at least 10,000 infants globally were affected by severe birth defects, with around 40% dying within their first year. The actual number may be much higher, considering stillbirths and miscarriages.

- **Withdrawal:** Thalidomide was banned and withdrawn from markets worldwide by 1962, following mounting evidence and international pressure.



Consequences and Regulatory Reforms

- **United States Response:** The US was largely spared from the tragedy due to FDA officer Frances Kelsey, who refused to approve thalidomide—citing missing safety data and emerging concerns about neurologic side effects. Her vigilance is credited with preventing significant US casualties.

- **Regulation Changes:** The scandal prompted major reforms worldwide:

- Drugs now require rigorous *teratogenicity* and safety testing before approval.

- Informed consent and patient information are now compulsory.

- Regulatory authorities such as the FDA were strengthened, setting global precedents for drug safety standards.

- Legislation like the 1962 US Kefauver Harris Amendment and the UK's 1968 Medicines Act were direct outcomes.

Mechanisms of Harm

- Thalidomide interrupts normal embryonic development, particularly if taken during 20–49 days of gestation. A single dose during this critical period can cause severe malformations.
- Researchers discovered thalidomide damages developing limbs and organs by interfering with molecular pathways—most notably affecting the SALL4 gene, essential for limb and organ development.

Ongoing Medical Role and Precautions

- **New Medical Indications:** Despite its history, thalidomide was "rediscovered" decades later for its anti-inflammatory and anti-angiogenic properties, especially in treating leprosy complications and multiple myeloma (a blood cancer).
- **Modern Use:** Thalidomide is now prescribed only under strict surveillance programs, with absolute contraindications in pregnancy. Modern protocols require contraception and regular monitoring for women of childbearing age, and caution even for men.
- **Safety Monitoring:** Monitoring includes pregnancy tests, neurological exams, and regular clinical follow-ups to minimize the risk of adverse effects and teratogenic exposure.

Lasting Legacy

Thalidomide's story underscores the critical need for *safety*, *transparency*, and *rigorous testing* in drug development. It set the benchmark for modern pharmaceutical regulation, patient advocacy, and vigilance in clinical practice. The ongoing availability of thalidomide under closely regulated conditions reflects both its therapeutic potential and the lessons learned from its tragic past.

3.Mechanism of Action

Thalidomide exhibits multiple pharmacological actions:

- **Sedative properties** via GABAergic modulation [5].
- **Anti-inflammatory** effects by inhibiting TNF-α [6].
- **Anti-angiogenic** activity by disrupting blood vessel formation, which is believed to underlie its teratogenicity [7].

Reason for Ban	Description
Severe Birth Defects (Teratogenicity)	Thalidomide caused catastrophic congenital malformations, especially limb deformities, when taken during pregnancy. More than 10,000 children were affected worldwide, primarily with shortened or absent limbs (phocomelia), eye, ear, and heart defects.
Lack of Adequate Safety Testing	At the time, thalidomide was approved based on animal toxicity but not for teratogenic (birth-defect-causing) effects. Drug safety regulations did not require fetal development studies.

Reason for Ban	Description
Peripheral Neuropathy in Adults	Adults taking thalidomide developed nerve damage (peripheral neuritis), manifesting as numbness and tingling in the hands and feet. This initially raised concerns about its general safety.
Over-the-Counter Availability	Thalidomide was widely and easily accessible in many countries without prescription, increasing the scale of fetal exposure and harm before dangers were recognized.
Delayed Recognition and Withdrawal	Many early adverse effects were denied or overlooked by the manufacturer and some authorities, leading to delayed drug withdrawal and prolonged public exposure.
Inadequate Drug Regulation	At the time, drug legislation was insufficient to prevent or respond rapidly to new drug risks. The thalidomide crisis directly prompted reforms in drug testing, approval, and monitoring worldwide.

4.Teratogenic Effects and Adverse Outcomes

Thalidomide-induced embryopathy results from its interference in limb bud development during early pregnancy [8]. Major anomalies included:

- Phocomelia
- Amelia
- Internal organ malformations
- Hearing and visual impairments

Animal studies revealed species-specific sensitivity, with rabbits and primates showing comparable effects to humans [9]

5.Global Impact and Regulatory Response

The thalidomide tragedy prompted major reforms in drug regulation:

- The Kefauver Harris Amendment in the USA (1962) enforced stricter safety and efficacy requirements [10].
- The establishment of pharmacovigilance systems in Europe [11].
- Expansion of teratogenic risk assessment protocols for new drugs [12].

6. Repositioning of Thalidomide

Despite its past, thalidomide has found new roles:

6.1 Leprosy

Approved by the FDA in 1998 for erythema nodosum leprosum (ENL) due to its immunomodulatory effects [13].

6.2 Multiple Myeloma

Used in combination therapies for relapsed or refractory cases [14].

6.3 Other Conditions

The conditions like HIV- related ulcers, Crohn's disease, graft- versus- host disease are investigated [15].

7. Pharmacokinetics and Metabolism

- Rapid oral absorption
- Extensive tissue distribution
- Undergoes non-enzymatic hydrolysis in plasma
- Half-life: 5–7 hours [16]

8. Risk Management Programs

Due to its teratogenicity, programs like S.T.E.P.S. (System for Thalidomide Education and Prescribing Safety) were created to ensure patient safety through pregnancy testing, informed consent, and restricted distribution [17].

9. Thalidomide Analogs

Second-generation analogs developed to reduce toxicity:

- **Lenalidomide**: More potent in myeloma with lower teratogenic potential [18]
- **Pomalidomide**: Used in resistant hematologic cancers [19]

10. Ethical and Legal Considerations

Thousands of victims sought compensation. While some countries offered settlements, many cases remain unresolved. The tragedy highlighted ethical concerns in clinical trials and pharmaceutical marketing [20].

11. Lessons Learned

Thalidomide catalyzed significant changes in:

- Drug approval processes
- Clinical trial ethics
- Public health policy

Its story underscores the importance of rigorous preclinical testing, especially in vulnerable populations like pregnant women [21].

12. CONCLUSION

The thalidomide tragedy is a landmark event in pharmaceutical history, symbolizing the catastrophic consequences of inadequate drug testing and insufficient regulatory oversight. Marketed as a safe sedative and antiemetic for pregnant women, thalidomide led to the birth of thousands of children with severe deformities, including limb malformations, blindness, deafness, and internal organ defects. This event prompted a global reevaluation of drug safety protocols, resulting in stricter preclinical testing requirements, more rigorous clinical trial regulations, and the establishment of modern pharmacovigilance systems. The legacy of thalidomide remains a cautionary tale that underscores the ethical responsibility of pharmaceutical companies and regulatory bodies to protect vulnerable populations, particularly during pregnancy. In recent years, thalidomide has been cautiously reintroduced for specific therapeutic purposes, including the treatment of erythema nodosum leprosum and multiple myeloma. This controlled use is supported by comprehensive risk management programs that include mandatory pregnancy testing, informed consent, and restricted distribution. The drug's reemergence, alongside the development of less toxic analogs like lenalidomide and pomalidomide, highlights its therapeutic potential when used responsibly. Nevertheless, the historical impact of thalidomide continues to influence drug development and approval processes worldwide, serving as a persistent reminder of the importance of rigorous safety evaluations, ethical clinical practices, and the

prioritization of patient welfare in all aspects of medical research and practice.

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